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ON THE MEASUREMENT OF MENTAL ACTIVITY THROUGH MUSCULAR ACTIVITY AND THE DETERMINATION OF A CONSTANT OF ATTENTION.

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IN 1886 Loeb published a preliminary communication in which he showed how muscular force could be used for the measurement of mental activity.[1] He found that the maximum pressure which the flexor muscles of the hand can exercise upon a dynamometer becomes smaller when the person attempts to do mental work simultaneously. The mental work in Loeb's experiments consisted in multiplying and reading. The more difficult the multiplication, the smaller the maximum pressure became. If P be the maximum pressure without mental work and p the maximum pressure with simultaneous mental work, the more attention the mental work requires the larger $P-p$ becomes.

If we assume further that P is the expression of the attention in the case that the whole available attention is given to muscular work, the expression $\frac{P-p}{P}$ represents the constant of attention for one kind of mental work. It is of interest to determine how this constant varies quantitatively for different kinds of mental work. At the request of Dr. Loeb, and under his direction, I determined the constant of attention for a number of various mental activities. The experiments were finished during the year 1895. Circumstances, however, have delayed their publication.

[1] LOEB: Muskelthätigkeit als Maass psychischer Thatigkeit. Arch. f. d. ges. Physiol., xxxix, p. 592.

Before I give the results of these experiments it will be necessary to describe the methods used.

I. On the Methods of determining Static Contraction.

I used Loeb's dynamograph (Fig. 1), designed for this special investigation. The subject grasps the handle, braces the palm of the hand against the post, then pulls as shown in the drawing.

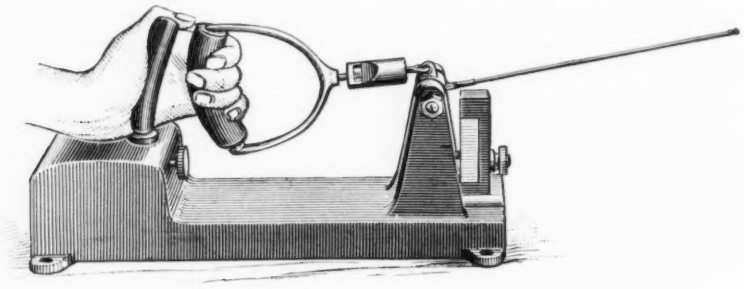

Figure 1.

The force of the hand works against the elasticity of a steel bar attached to a movable axle which has a lever. The axle, bar, and lever are all in one piece, which is held by steel screw points. The steel bar rests against a wedge. The length of the part strained can be varied by moving the wedge to any place on the scale.

Fig. 2 is a drawing of the steel wedge and axle. The distance between the handle and the post can be adjusted to hands of different sizes. This distance is kept constant for the same subject. As the bar bends, the axle turns and the lever is raised.

The dynamometer was calibrated by suspending weights to the hooks on the axle, the force being directed by a pulley, in the direction in which the pull is made. The height to which the lever was raised for each additional kilogram was traced on the smoked drum of a kymograph. In this manner a scale was made by which every kilogram of force applied to the dynamometer could be measured directly.

Figure 2.

The static contraction is a contraction caused by a constant innervation. The subject grasped the handle of the dynamometer and gave a constant maximum innervation to the muscles of the hands until the beginning of fatigue was felt, a curve being traced on the revolving cylinder. A time-marker connected with a second's pendulum registered the seconds. The ordinates of the curve represent the force; the abscissæ, the time. The area, or product of the mean ordinate by the number of seconds, expresses the static contraction in terms of kilogram-seconds.

The static work varies as the mean pressure, as the following figures show.

Right Hand.		
Mean ordinate, in kilos.	Number of seconds.	Static contraction in kilogram-seconds.
24.0	34	816.0
16.1	49	738.9
11.3	83	937.9
4.6	170	782.0
3.8	286	1086.0

The abscissæ increase as the ordinates decrease. The maximum static contraction expressed in kilogram-seconds is when the mean ordinate in the series is smallest. Yet the static contraction is greater with the average ordinate at 11.3 than at 4.6 kilograms. So the static contraction is not always greatest with the smallest ordinate. It is a function of both time and force.

The chief source of error in obtaining the maximum constant innervation is lack of attention. The slightest distraction shows a corresponding decrease in the height of the ordinate. With some subjects, the maximum innervation is not given until after several trials, although the subject may think so in the first trial. In all cases the second curve is a little higher than the first. The tonus of the muscle is increased slightly by exercise.

I observed that, whenever the maximum innervation was given to the hand, several groups of muscles were innervated at the same time; as, for example, the muscles of the resting hand, of the face,

TABLE I.

	Right Hand.		Left Hand.	
	Innervation of one hand alone.	Innervation of both hands.	Innervation of one hand alone.	Innervation of both hands.
Maximum ordinate . .	27.0 kilos.	25.5 kilos.	25.5 kilos.	26.0 kilos.
	29.0	29.0	24.0	25.5
	26.0	28.0	25.0	25.0
	27.0	27.0	28.0	25.0
	24.0	26.5	23.0	25.0
Mean	26.6	27.2	25.1	25.7
Ordinate at 10 seconds	25.0 mm.	24.0 mm.	22.0 mm.	24.0 mm.
	24.5	27.0	21.0	22.5
	26.0	28.0	23.0	24.0
	27.0	26.0	26.0	21.0
	22.0	24.0	22.0	24.0
Mean	24.9	25.8	22.8	23.1
Minimum ordinate . .	19.0	22.0	23.0	23.0
	23.0	26.0	22.0	23.0
	23.0	22.5	22.0	20.0
	23.0	25.0	25.0	21.0
	23.0	22.0	21.0	22.0
Mean	22.2	23.5	22.8	23.1
Mean ordinate of curve	23.2	23.8	23.5	24.3
	25.5	27.3	22.3	23.6
	24.7	25.1	23.0	22.2
	25.0	26.0	26.3	22.6
	23.0	24.1	22.0	25.5
Mean	24.2	25.2	23.4	23.6

and of the jaws. The subject is quite unconscious of this, since his sole purpose is to produce the maximum force. This led me to experiment to find out if the effect would be greater when I gave a maximum innervation to both hands simultaneously than to one alone.

Using the kilogram scale, I measured the ordinates of each curve. I have given, in Table I, four ordinates for each curve, the maximum ordinate, the ordinate at ten seconds, the minimum, and the mean ordinate. The corresponding ordinates in both cases are arranged in parallel columns. In tracing each curve, the handle of the dynamometer was dropped the moment fatigue of the muscles was perceived.

One sees that the corresponding ordinates are usually somewhat larger in the cases in which both hands were innervated at the same time; the difference would have been greater in all probability if in innervating one hand alone I had succeeded in inhibiting all impulses to the other hand.

I repeated the same experiments, varied only by holding a thirty-pound weight in one hand while pulling the dynamometer with the other. The results were practically the same as in the preceding experiments. I give in Table II the mean of each set of ordinates out of five experiments with each hand. The innervations of the pulling hand are more constant when the other hand is holding a weight. This is the only difference in the two series of experiments.

TABLE II.

	Right Hand.		Left Hand.	
	Innervation of left hand.	Holding 30 lb. weight.	Innervation of left hand.	Holding 30 lb. weight.
Mean maximum ordinate	26.5 kilos	27 kilos	25 kilos	25.6 kilos
Ordinate at 10 secs. .	26.8 mm.	27 mm.	23.4 mm.	24.3 mm.
Minimum ordinate .	21.2	23.5	21.4	23.3
Mean ordinate . . .	23.7	25.6	22.8	23.8

It seems probable that the effect of the innervation to the hand varies inversely as the number of inhibitions given to the other mus-

cles at the same time. A child innervates several groups of muscles in his first attempts to use one set of muscles. All control seems to depend on inhibition impulses.

II. Determination of the Constant of Attention for Various Mental Activities.

The maximum static innervation of the hand is arbitrarily selected here as a measure of other voluntary activities simultaneously attempted. I do not mean that a muscular equivalent of mental activity can be determined in the sense in which we determine the mechanical equivalent of heat. Loeb found that the maximum force of the hand decreased in proportion to mental work. The decrease of muscular force during mental activity may be due to an act of inhibition of innervations, or may be a result of a division of the constant innervation energy between two simultaneous activities, but in either case the relation of the decrease to the intensity of mental activity is primarily a function of attention. There can, however, be no adequate explanation of attention while so little is known of the physiology of the elements in the nerve centres. Therefore I shall not attempt to explain these facts, but I hope to contribute something to the physiology of attention.

In order to obtain the maximum static contraction curve, the constant undivided attention is necessary, and, if the element of fatigue does not enter in, the innervation will depend upon the concentration of attention. Therefore, according to Loeb, the ratio of the decrease in the maximum constant muscular innervation accompanied by a mental activity, to the original maximum constant innervation alone, gives the constant of attention for any given time. The determination of the constant of attention for various kinds of mental work, affords a method of comparing the degree of concentration of attention required in different kinds of activity.

If P equals the force of the hand at any given second, in the maximum static curve, p, the force of the hand at the same time when accompanied by mental activity, then the constant of attention, $A = \frac{P-p}{P}$.

A. **Constant of Attention in Registration of Rhythmical Motions.** — 1. In each experiment three curves are traced. Thus, curves (1) and (3) in Fig. 3 are maximum static curves, the former recorded at the beginning, the latter at the end of the experiment. Curve (2) records

the attempt to give a constant muscular innervation to the hand while observing with the eye the vibration of a second's pendulum, and registering each time the bulb reaches its maximum amplitude on either side of the centre. It is at this moment of maximum amplitude that the electric connection is made in the pendulum, and the time-marker records a second. If the tracings of the pen and those of the time-marker coincide, the observations are accurately recorded, showing good attention on the part of the observer. In Fig. 3 (2) the subject begins the mental work first, and then attempts the muscular, while the attention on the observation and registration is continued.

The pneumatic pen of Marey's tambour registered each observation. Two closed rubber tubes connected with the tambour by a

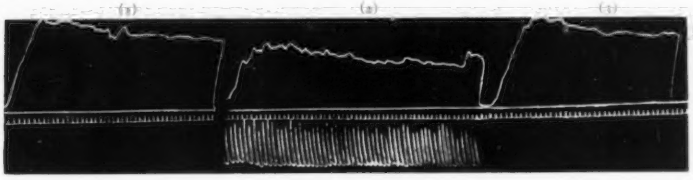

FIGURE 3.

glass **T**-tube. The pneumatic pen recorded each time the rubber tube was pressed. The lever of the dynamometer, the time-marker, and the pen were arranged in the same vertical line at the beginning of each experiment.

The second maximum static curve (Fig. 3, (3)) was traced to make sure that the decrease in the preceding curve was not due to fatigue. Each curve was continued until the subject was conscious of the beginning of fatigue; a period of rest was then allowed. Every precaution was taken to eliminate fatigue.

I have given in the following tables the results of the last ten experiments with each hand, recorded in Fig. 3. The first experiments gave very irregular results, but after a little practice, I could register observations and pull the dynamometer at the same time much more accurately.

In these tables, four constants, obtained by substituting ordinates, represent the force for the given time. In the formula for the constant of attention, $A = \frac{P-p}{P}$; for the value of P, the mean of the corresponding ordinates in curves (1) and (3), Fig. 3, is used; for

p, the ordinates of curve (2), corresponding to the same second as those taken in (1) and (3), are employed.

If the attention were constant in each experiment, the ordinate would be the same for each second and the curves would be a straight line. Since there are fluctuations of attention in each experiment I have measured the constant for the beginning, the end, at ten seconds, and for the mean of the ordinates at the several times. The maximum ordinate in curve (2) is often higher because the attention is turned from the mental work when beginning to pull the dynamometer; at the end, the minimum ordinate may be lower than necessary in order to do the registering accurately. The ten-second constant is freer from this error, and, in most cases, is nearer the mean constant.

It should be remarked that where there is inaccuracy in the registration of the vibrations of the pendulum, there is a corresponding increase in the muscular effect. Sometimes, when the subject begins the muscular work after beginning the registration, the lever of the dynamometer will reach nearly its maximum for a second or two, then drop suddenly as the mental work is begun accurately. In beginners in these experiments, there is either a rapid oscillation from one kind of work to another or the innervations given to the registering hand are transmitted to the pulling hand, as the impulses are periodically summed. Probably both these influences are felt.

In Table III (*a*) I have given the result of ten experiments performed upon myself after I had had some practice in experimenting. Table III (*b*) gives the results obtained from different subjects.

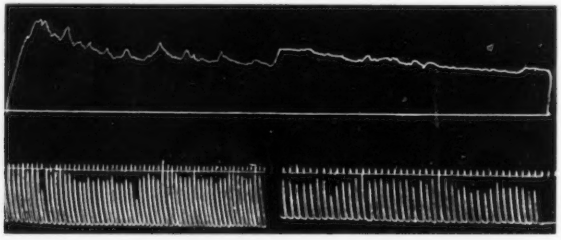

FIGURE 4.

All the curves obtained by the left hand during registration are much more regular than those obtained by the right hand; compare Fig. 4. These irregularities are due, probably, to a summation of stimuli

TABLE III.

(*a*)

	Right Hand.			Left Hand.		
	P.	f.	$A = \frac{P}{P} f$.	P.	f.	$A = \frac{P}{P} f$.
Ordinates at ten seconds.	30.5	25.0	....	25.0	21.0	....
	32.0	18.0	....	22.5	16.0	....
	25.5	20.0	....	22.0	19.0	....
	30.0	32.0	....	25.0	19.0	....
	25.5	21.0	....	22.7	18.0	....
	25.7	18.0	....	22.5	18.0	....
	28.5	18.0	....	23.0	18.0	....
	24.0	19.0	....	22.0	15.0	....
	26.7	22.0	....	20.7	17.5	....
	28.2	25.0	....	24.7	19.5	....
Mean . .	27.6	20.8	0.25	22.9	18.1	0.20

(*b*) *Constants obtained from different subjects.*

Right Hand.

Subject No.	Max. A.	10 sec. A.	Min. A.	Mean A.
2	.09	.12	.33	.32
3	.12	.25	.48	.29
4	.16	.17	.55	.37
5	.13	.35	.53	.34
9	.32	.38	.57	.44

on pressing the rubber tube with the left hand. The stimuli in the rhythmical recording do not pass to the left hand so readily when the right hand is recording, but when the left hand is recording, the rhythmical impulses pass to the right hand as readily as to the left. Physiologically, it is not known why the stimuli seem to pass with

less resistance along the course most used. In one curve (Fig. 5 (2)), the summation is nearly regular for every five seconds. These irregularities are very marked with most beginners. In some cases the hand on the dynamograph follows the rhythm of the pressing of the rubber tube. There was a tendency for the one registering to press harder in the attempt to keep the force of the dynamograph constant. The other subjects always used the right hand, so I think there would be this difference in two hands in most cases. I experimented most with No. 3 (see Table III), nine times — and the ten-second and mean constant of that subject is nearer that of my own. I should expect, however, to find as much difference in this constant for different persons as in the time reaction. I have given one subject the same number in all the series of experiments.

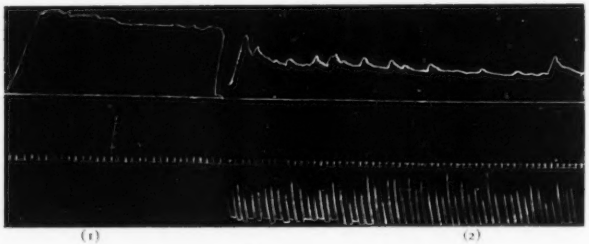

FIGURE 5.

2. The next series of experiments is like the preceding, varied only by pressing alternately two tubes in registering the observations. It required somewhat greater effort of attention in keeping the hand alternating from one tube to the other, and registering at the same time, as shown in curve (2), Fig. 5, when compared with (2) of Fig. 3.

Comparing these constants of attention with the corresponding ones of the first registration, the latter are without exception markedly higher, both in experiments made upon myself and upon others. It may be interesting to note that in spite of the great difference in the maximum ordinate of the six subjects, three of the mean constants are .42, one .41, and one .34.

The same errors, and consequently the same irregularities, appeared in these curves as in the former ones; namely, those irregularities caused by the oscillation of attention from one activity to the other, or by the periodical summation of innervations from the

TABLE IV.

(*a*) *Registration of vibration by pressing two tubes. Visual observation.*

	Right Hand.			Left Hand.		
	P.	p.	$A = \frac{P-p}{P}$.	P.	p.	$A = \frac{P-p}{P}$.
Ordinates at ten seconds	27.2	13.0	....	23.0	13.0	....
	26.0	12.0	....	24.7	15.0	....
	26.5	8.0	....	24.5	18.0	....
	23.5	15.0	....	25.5	14.0	....
	24.5	14.0	....	27.0	15.0	....
	21.5	10.0	....	23.5	14.5	....
	22.5	10.0	....	23.5	11.5	....
	23.5	9.0	....	24.0	17.0	....
	26.5	14.5	....	26.2	15.0	....
	24.2	13.0	....	20.5	13.0	....
Mean. . .	24.3	11.8	0.48	24.2	14.6	0.39

(*b*) *Constants obtained from different subjects.*

Right Hand.

Subject. No.	Max. A.	10 sec. A.	Min. A.	Mean A.
2	× .20	.60	.69	.42
3	× .17	.32	.56	.34
4	× .22	.33	.61	.42
5	× .29	.40	.80	.42
9	× .61	.70	.75	.70

rhythmical pressing with the other hand. The latter irregularity was more marked in these experiments than in the first ones. It appeared with the right hand pulling the dynamometer as in the other series. Probably sufficient practice would eliminate these.

3. I determined whether the constants in registering by two

tubes would be less if the observations of the vibrations were made by listening to the ticking of the pendulum rather than by visual observation.

TABLE V.

Registration by pressing two tubes, auditory observation.

	Right Hand.			Left Hand.		
Ordinate.	P.	p.	$A=\frac{P-p}{P}$.	P.	p.	$A=\frac{P-p}{P}$.
Mean Max. .	27.5	20.4	0.26	25.4	17.1	0.35
10 sec. . .	24.2	17.0	0.29	23.5	14.4	0.38
Min. . . .	20.2	14.4	0.28	20.5	11.4	0.44
	Mean $A=0.28$.			Mean $A=0.38$.		

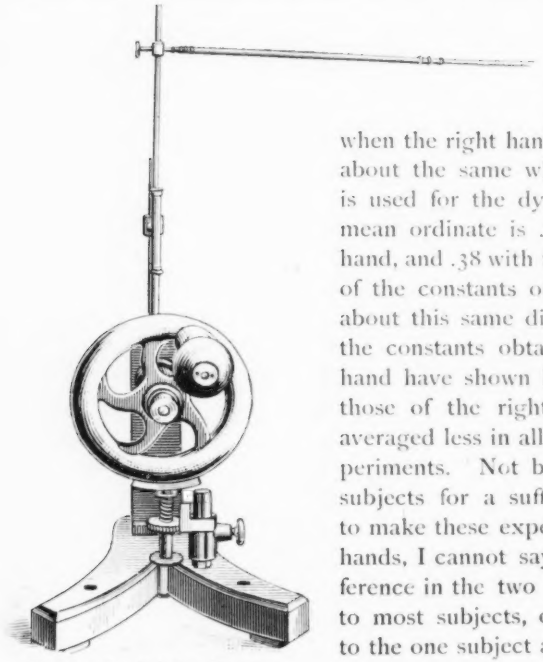

Figure 6. Friction Machine.

The constants are less in auditory observation than in visual, when the right hand only is used, but about the same when the left hand is used for the dynamometer. The mean ordinate is .28 with the right hand, and .38 with the left hand. All of the constants of each hand show about this same difference. Most of the constants obtained with the left hand have shown less variation than those of the right hand, and have averaged less in all of the former experiments. Not being able to have subjects for a sufficiently long time to make these experiments with both hands, I cannot say whether this difference in the two hands is common to most subjects, or simply peculiar to the one subject alone.

4. I combined muscular effort with the registration by substituting a friction machine for the tambour. The friction machine (Fig. 6) consists of a wheel and axle to which is attached a jointed vertical rod carrying a long lever. At each revolution of the wheel the rod moves up and down and the lever traces an harmonic curve. The subject turned the wheel one half of a revolution at each observation. Under the wheel is a brake block, which can be lowered or raised by a thumb screw. The brake block is supported on a coarse, stiff, steel spring, and the closer the brake block is pressed against the wheel, the greater the number of units of friction produced between the two through the elasticity of the spring.

I have given the constants obtained by taking the mean of five experiments with each hand when the friction was, 0, 1, 5, and 8, as indicated by the scale beside the brake block

TABLE VI.

Registration of vibration by friction machine.

Visual Observation.

	Right Hand.		Left Hand.	
I	Mean constant of Max. *A.*	10 sec. *A.*	Mean constant of Max. *A.*	10 sec. *A.*
F0	.30	.46	.33	.37
F1	.32	.42	.28	.62
F5	.16	.42	.27	.35
F8	.13	.27	.21	.32
	Min. *A.*	Mean A.	Min. *A.*	Mean *A.*
F0	.62	.46	.50	.45
F1	.50	.40	.47	.37
F5	.46	.35	.40	.34
F8	.29	.26	.43	.31

The constants are greater than in the previous experiments when there is no friction, but as *F* increases, the constants decrease. This

decrease in the constants depends upon the increase in the innervation of the recording hand in order to overcome the resistance of the wheel. This is the same phenomenon mentioned before: namely, that the effect in the hand pulling the dynamometer is greater if the same muscles in the other hand are innervated at the same time. Therefore, in $A = \frac{P-p}{P}$, p increases with F; hence A decreases when F increases.

One observes the same difference in the constants of the two hands even in a more marked degree in this set of experiments. The impulses passing to the left hand in overcoming friction in turning the wheel affect the right hand more while that hand is pulling the dynamograph than when the left hand is pulling. Therefore the constants for the right hand are much less than those for the left.

B. **Constant of Attention in the Observation of Coincidence of Two Vibrating Pendulums.** — The second pendulum and the pendulum of a metronome were set vibrating in different periods of time. A lever recorded the vibration of the metronome. The metronome pendulum was lengthened and marked with red, and so placed in relation to the second pendulum that the tracings of both would show coincidence at the same time that the coincidence could be seen by the observer. When the subject observed the coincidence he pressed a rubber tube of Marey's tambour. All the levers being arranged in the same vertical line at the beginning, the tracings show whether the observations were accurate.

I give the results of three sets of experiments made in different ways: (*a*) the observation was made by the eye directly; (*b*) the subject looked through a small dark tube which shut off most of the visual field except at the place of coincidence; (*c*) every fifth vibration of the metronome, and every second vibration of the second pendulum were registered. Five experiments were made with both hands in each case.

I found it very difficult to register accurately and to pull the dynamometer even after some practice; none of the first (*a*) series was accurate. Most of the next series (*b*) were nearly accurate. It was easier to see the coincidence through the tube, although it required greater effort in accommodating the eye to the tube. Probably this may be the reason that the constants are somewhat higher in (*b*).

In the last series (*c*) the mental effort of memory, as well as that of observation, was involved for the first time. It required the greatest effort of attention to remember the counts of both pendulums and do any muscular work at all. In nearly all the experiments the vibration of one of the pendulums would be registered accurately, and that of the other registered irregularly. There was more regularity in the form of the curves and less difference in the results of the two hands in all of these experiments than in the former ones.

TABLE VII.

Constants of attention in registration of coincidence of two vibrating pendulums.

(*a*)	Right Hand.			Left Hand.		
Mean Or.	P.	p.	$A = \frac{P-p}{P}$.	P.	p.	$A = \frac{P-p}{P}$.
Max. . . .	26.1	20.3	.21	23.6	17.8	.24
10 sec. . .	24.1	16.8	.30	22.3	14.0	.37
Min. . . .	21.4	10.4	.51	19.9	10.3	.51
	Mean A = .34			Mean A = .35		
(*b*) *Observation through a tube.*						
Max. . . .	26.3	17.6	.33	22.4	14.6	.34
10 sec. . .	23.5	15.3	.34	20.9	12.2	.41
Min. . . .	22.9	9.8	.57	19.0	9.8	.48
	Mean A = .41			Mean A = .42		
(*c*) *Registration of 5th vibration of metronome and 2d vibration of pendulum.*						
Max. . .	25.7	13.2	.48	22.7	11.8	.48
10 sec. . .	24.9	9.6	.61	21.7	9.4	.56
Min. . . .	19.2	6.6	.65	17.9	6.2	.65
Mean. . .	22.0	8.9	.59	20.0	8.3	.58

C. **Determination of the Constant of Attention in Reckoning.** — When reckoning, I found myself whispering each step in the process, and the harder I pulled the dynamometer, the greater was the tendency to whisper, and the greater the effort to remember. The whispering and the writing of the results produced great irregularities in the curves. I finally obtained constants from two series of five experiments each, for both hands. In the first (*a*) I performed multiplication of the numbers from 12 to 20, as 14×13, 14×15, etc., in every combination, until I was conscious of the beginning of fatigue. The second series (*b*) was done in the same way, with numbers from 20 to 30. In both series, the eyes were closed, there was no whispering, and the results were recorded from memory after each experiment. Then I tried to eliminate all the effects from other muscular impulses, such as whispering, writing, and visual perception.

The constants in (*c*) were obtained in the same way as those of (*a*) and (*b*), by multiplying numbers from 60 to 70; also those in (*d*) by simply adding by 12's, 9's, 8's, etc.

I found it required less effort in reckoning if the figures were before the eye, and the constants in (*c*) were obtained in that way. I could not repeat the reckoning in (*a*) or (*b*), since the practice with those numbers had made it less difficult, so I took the numbers from 30 to 40.

The constants in (*b*) are, on the whole, greater than those in (*a*), especially the mean constant. In the other series they are smaller, although the numbers are larger.

The constants obtained in adding (*d*) are considerably smaller, as we should expect, as the mental effort is less.

Although it seemed much easier to reckon with the eye upon the figures and to repeat each process to myself, the constants obtained with the right hand are about the same as those in (*a*), and less with the left. The numbers were larger (30–40) but the mental effort was about the same. The reason the constants with the left hand are smaller in this particular case I cannot explain. In reckoning all of the other series the mean constants obtained with the left hand were a little higher than those obtained with the right hand. The innervation of the vocal cords and muscles used in speech must have interfered with the innervations of the left hand.

The effort in memory is less with the figures before the eyes, yet the attention in observation is another factor which has a much greater effect on attention than one realizes.

TABLE VIII.

CONSTANT OF ATTENTION IN RECKONING.

(*a*) *Multiplication of numbers from* 11 *to* 20 *with eyes closed.*

	Right Hand.			Left Hand.		
Mean ordinate.	P.	p.	$A=\frac{P-p}{P}$.	P.	p.	$A=\frac{P-p}{P}$.
Max. . . .	25.3	11.9	.52	23.2	10.2	.56
10 sec. . .	22.9	10.2	.55	21.6	9.3	.56
Min. . . .	19.9	8.8	.55	18.3	7.4	.59
Mean . . .	22.0	10.0	.54	20.4	9.0	.55
	Four errors out of 22 problems.			Four errors out of 18 problems.		

(*b*) *Multiplication of numbers from* 20 *to* 30, *eyes closed.*

Max. . . .	26.1	12.1	.53	23.7	10.8	.54
10 sec. . .	23.5	9.4	.60	21.9	9.8	.55
Min. . . .	20.5	7.9	.60	18.4	6.7	.63
Mean . . .	23.2	9.1	.59	20.5	7.9	.61
	Four errors out of 20 problems.			Six errors out of 20 problems.		

(*c*) *Multiplication of numbers from* 30 *to* 40. *Results registered. Eyes follow the figures.*

	Max. A.	10 sec. A.	Min. A.	Mean A.
Right Hand . .	.50	.54	.63	.54
Left Hand . . .	.46	.35	.43	.38

(*d*) *Adding by* 12's, 8's, 9's, *etc., eyes closed.*

	Max. A.	10 sec. A.	Min. A.	Min. A.
Right Hand . .	.40	.44	.32	.39
Left Hand . . .	.46	.48	.46	.47

(*e*) *Multiplication of numbers from* 11 *to* 20.					
Subject No.	Ratio of error.	Max. *A.*	10 sec. *A.*	Min. *A.*	Mean *A.*
2	¾	.24	.31	.41	.30
3	....	.65	.65	.62	.64
6	½	.20	.20	.22	.23
8	½	.13	.20	.27	.20
10	....	.40	.43	.48	.44

(*f*) *Multiplication of numbers from* 60 *to* 70.				
Right Hand .	Max. *A*, .46	10 sec. *A*, .48	Min. *A*, .46	Mean *A*, .47

D. **Constant of Attention in Reading and Writing.**—In this series I determined the constants with the right hand alone. I read an article not very difficult to comprehend from a sociological journal, and determined the constants as before. The following table (*a*) shows that the constants are smaller than those in reckoning.

TABLE IX.

(*a*)

	Max. *A.*	10 sec. *A.*	Min. *A.*	Mean *A.*
Right Hand . .	.34	.30	.36	.34
" " . .	.38	.37	.30	.38

In (*b*) are seen the results of a series of experiments where I used all those coördinated muscles necessary in writing without doing other mental work. I made short straight lines, one after another, all the time I was pulling the dynamometer. Thus I determined the constants for those complex coördinated motions.

This activity requires about the same degree of attention as that in the other two series. The constants for the right hand may be a little higher on account of the greater effort in writing with the left hand. I observe here, that the greater the muscular effect in pulling the dynamometer, the longer the marks, and the harder the other

hand would press on the paper in writing. Accordingly the more the subject inhibited such impulses and wrote naturally, the less the muscular work done. I believe this explains the lower constants of attention obtained from other subjects in this series of experiments(*c*).

(*b*) *Constants in writing.*

	Max. *A.*	10 sec. *A.*	Min. *A.*	Mean *A.*
Right Hand . .	.34	.41	.40	.35
" " . .	.36	.30	.36	.33

(*c*)

Subj. No.	Max. *A.*	10 sec. *A.*	Min. *A.*	Mean *A.*
2	.20	.33	.33	.22
3	.28	.25	.31	.24
11	.08 ×	.25	.46	.24

E. **Constants Varied by Beginning Muscular Activity First.**—In all the former determinations, the muscular activity was begun while the mental activity was going on. By reversing this order I found as Loeb had done before that in most cases the corresponding constants were markedly less. The difference is more marked in some subjects than in others, but in all cases the mean constant is less if determined by beginning the muscular activity first.

As I mentioned before, among the sources of errors, a subject often transfers most of the attention from the mental to the muscular work when he first begins to pull the dynamometer, and this is the reason the maximum constants are not more accurate.

The effect of the order of the two activities on the constants of attention may have some theoretical importance. The following tables give the constants side by side, obtained under each condition. The inhibitory effect of the mental activity upon the muscular work is less when the muscular innervation is begun first. Hence the constant of attention is much less for the same activity, as the table shows.

TABLE X.

	Muscular act. 1st. 10 sec. *A.*	Mental act. 1st. 10 sec. *A.*	Muscular act. 1st. Min. *A.*	Mental act. 1st. Min. *A.*	Muscular act. 1st. Mean *A.*	Mental act. 1st. Mean *A.*
(*a*) *Registration of vibration of pendulum, 2 tubes.*						
R. H. .	.22	.48	.33	.49	.23	.41
L. H. . .	.21	.39	.42	.42	.30	.34
(*b*) *Observation of coincidence of two pendulums.*						
R. H . .	.31	.34	.38	.57	.24	.41
L. H. .	.11	.41	.37	.48	.31	.42
(*c*) *Reckoning.*						
R. H. .	.26	.55	.56	.55	.42	.54
L. H. .	.13	.55	.14	.63	.39	.61
(*d*) *Writing.*						
R. H. .	.10	.41	.13	.40	.01	.35
L. H. .	.25	.30	.05	.36	.14	.33
(*e*) *Registration of vibration of pendulum.*						
Subj. No.	Muscular act. 1st. 10 sec. *A.*	Mental act. 1st. 10 sec. *A.*	Muscular act. 1st. Min. *A.*	Mental act. 1st. Min. *A.*	Muscular act. 1st. Mean *A.*	Mental act. 1st. Mean *A.*
R. H. 3	.34	.34	.16	.32	.56	.56
L. H. 4	.27	.42	.10	.33	.44	.61
(*f*) *Reckoning.*						
R. H. 2	.28	.30	.20	.31	.16	.41
" " 3	.10	.64	.06	.62	.25	.64
L. H. 8	.01	.20	.06	.20	.14	.27

TABLE XI.

Fatigue curves.

	Muscular activity alone.			(*a*) Muscular and mental activity. Registration of rhythms.		
	Mean or.	No. sec.	Kilo. sec.	Mean or.	No. sec.	Kilo. sec.
Right Hand .	K 21.2	79	1674.8	10.0	157	1570.0
" "	15.2	72	1049.4	8.0	182	1456.0
" "	18.4	101	1858.4	13.1	114	1493.4
" "	22.3	63	1398.6	125.0	86	1075.0
" "	24.0	13	312.0	15.0	114	1710.0
Left Hand .	21.5	77	1655.5	11.7	192	2246.4
" "	17.6	76	1337.6	12.9	212	2734.8
" "	16.5	71	1171.5	11.1	116	1287.6
" "	15.5	72	1116.0	6.7	274	1835.8
" "	....	....	....	13.4	146	1956.4
				(*b*) Reckoning.		
Right Hand .	12.0	130	1560.0	10.5	229	2404.5
" "	14.5	68	986.0	8.3	298	2473.4
" "	16.0	115	1840.0	7.4	285	2109.0
" "	17.5	107	1872.5	6.0	252	1512.0
" "	7.6	228	1732.8	....	....	....
Left Hand .	10.4	101	1050.4	9.4	303	2848.0
" "	10.8	202	2181.6	9.0	298	2682.0
" "	16.0	76	1216.0	8.1	270	2187.0
" "	8.6	206	1771.6	....	....	....
" "	14.8	88	1302.4	....	....	....

III. Fatigue.

Fatigue entered incidentally into these experiments, and I will give some facts observed. It was found without exception that the feeling of muscular fatigue sets in much later when the muscular activity is accompanied by mental activity. The difference in time was from 15 to 33 per cent.

Other experiments were conducted in the manner just described, but the subject continued the work in all cases until fatigued, instead of stopping the moment fatigue began to be felt.

Table XI gives the static work alone and when accompanied by mental work, in kilogram-seconds.

The tables show that in twelve cases out of fifteen, the static contraction in kilogram-seconds is greater during mental activity. Since the work done in each case is proportional to the area of the curve, the actual muscular work done is the greater when accompanied by mental activity. There are two probable causes for this: (1), a lower mean ordinate; (2), a higher threshold value for the sensation of fatigue during mental work than during muscular activity alone. It is a matter of common experience that one does not feel physical fatigue or any pain so soon when the attention is given to some one activity.

The increase in the threshold value for the perception of fatigue would take place whether the origin of fatigue was in the periphery or in the central nervous system. If the energy of all the innervation from the centres has one common source, the origin of fatigue, in these experiments, must be in the periphery; otherwise the mental work would be done at the expense of the muscular work; but the origin of fatigue is not in the loss of innervation energy in the centre, but in the muscle tissue itself.

IV. Conclusion.

I will make a brief summary of the quantitative results of my investigations by giving a comparative table of the constants of various activities arranged in the order of the magnitude of the mean constants. A study of the tables shows that the constant of attention for any activity increases with —

1. Effort of accommodation of the special sense organs.
2. Effort in coördination of the muscles.
3. Effort of the memory.
4. Number of simultaneous activities.

CONSTANTS OF ATTENTION FOR VARIOUS MENTAL ACTIVITIES FROM ONE SUBJECT.

	R. H.	L. H.
Registration of Vibration of Pend. by one Tube; Visual Per.	·23	·21
" " " " " two Tubes; Auditory Per.	·28	·38
Direct Observation of Coincidence of two Pend. and Register	·34	·35
Reading	·34	.
Writing	·35	·33
Strained Visual Perception	·38	. .
Adding Numbers	·39	. .
Observation of Coincidence of two Pend. through Tube and Register	·41	·42
Registration of Vibration of two Pend. by two Tubes (Visual)	·46	·34
Rhythmical Rotation of Wheel with Pend.	·46	·45
Multiplication of Numbers from 60 to 70	·47	. .
" " " 12 to 20	·54	·55
" " " 20 to 30	·59	·61
Counting of Register of 5th Vibration of Metronome and 2d Vibration of Pend.	·59	58

MEAN CONSTANTS OF ATTENTION FROM VARIOUS SUBJECTS.

Subject.	Register of vibrations of pend., one tube.	Register, two tubes.	Writing.	Visual perception.	Auditory perception.	Reading.	Repeating poetry.	Adding.	Multiplying numbers from 18 to 20	Observation of coincidence of two pend.
2	.32	.42	.22	....	....	....	....	....	.36	....
3	.29	.34	.24	.28	.30	50	....	....	.64	.19
4	.37	.42	....	....	....	.38	....	....	....	.55
5	.34	.42	....	....	....	....	....	....	....	....
6	....	....	....	....	....	....	.09	....	.23	....
7	....	....	....	....	....	.27	....	.39	....	.51
8	....	....	....	....	....	....	....	....	.28	....
9	.44	.70	....	....	....	....	....	....	....	....
10	....	....	.44	....	....	....	.46	....	.44	.10
11	....	....	.24	.09	.04	....	....	....	....	....

From a study of the curves for the two hands, I must conclude that the innervations to perform rhythmical contractions given to the left

hand, while the right hand is innervated to pull the dynamometer, are communicated to the right hand and influence the form of the curve, while innervations to perform rhythmical contractions given to the right hand, while the left is pulling the dynamometer, are not transmitted, or, at least, are transmitted much less markedly to the left hand. Whatever be the physiological explanation, frequent repetition eliminates this difference in the two hands.

After a certain amount of practice, and with care to have like conditions in every case, I believe that the mean constant of attention for any mental activity can be determined for every subject with as slight variations as the personal equation in time reaction.

In conclusion, I wish to express my gratitude to Professor Loeb, for the kind assistance and the many valuable suggestions that I have received from him during the course of my work. My thanks are also due to a number of my fellow students who served as subjects for experiment.

THE INFLUENCE OF BILE AND BILE SALTS ON PANCREATIC PROTEOLYSIS.

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THE natural commingling of bile and pancreatic juice in the duodenum is strongly suggestive of harmony of action, and it might reasonably be assumed that in pancreatic proteolysis the presence of bile would be in no wise inimical. Indeed, such few observations as have been recorded tend to show, as a rule, that the proteolytic action of the pancreatic enzyme is not materially impeded by the presence of bile or its constituent salts. Thus, many years ago Heidenhain [1] observed that when an aqueous solution of dried pig's bile was added to a glycerin extract of the pancreas, the proteolytic power of the latter was not diminished, but apparently increased. A similar stimulating effect was observed on addition of a 1 per cent solution of sodium glycocholate to the enzyme-containing solution. The few experiments then made were purely qualitative ones, proteolytic power being determined simply by noting the rate at which flocks of fibrin were dissolved. The results, however, were sufficiently convincing to lead Heidenhain to the conclusion that "the salts dissolved in the bile have an influence similar to that of sodium chloride." Some years later Lindberger [2] found that the well known inhibitory action of organic acids upon trypsin-proteolysis may be overcome, to some extent at least, by the presence of bile salts. Thus he observed that the presence of 1–2 per cent of bile with some sodium chloride would enable a trypsin-solution containing 0.02 per cent of lactic acid to digest fibrin as rapidly as a neutral solution of the enzyme; indeed, as rapidly as an alkaline solution, provided the content of alkali was not too great. If, however, the proportion of lactic acid was raised to 0.05 per cent, then bile and sodium chloride were without avail in stimulating proteolysis. Experiments made by the writer [3] some years ago likewise tended to

[1] HEIDENHAIN: Archiv für die ges. Physiol., 1875, x. p. 579.

[2] LINDBERGER: Jahresbericht für Thierchemie, 1883, p. 282.

[3] CHITTENDEN and CUMMINS: Influence of bile, bile salts, and bile acids on amylolytic and proteolytic action. Amer. chem. journal, 1885, vii. p. 50.

show that the presence of bile in a pancreatic extract containing combined salicylic acid may increase somewhat the rate of trypsin-proteolysis over that of the acid mixture alone. It was also shown at the same time that the addition of bile, even to the extent of 10 per cent, to neutral or alkaline pancreatic juice modifies only slightly the rate and extent of proteolysis; under some conditions inducing a slight stimulation and under other conditions a more marked inhibition of proteolysis. It was likewise observed that the deleterious action of combined hydrochloric acid upon trypsin-proteolysis was not overcome by the addition of bile. A few experiments reported by Martin and Williams[1] have also tended to indicate that bile and bile salts may stimulate somewhat the rate of pancreatic proteolysis.

A careful survey of the results, and of the conditions under which the results were obtained, recorded up to this time, led the writer to the conclusion that the addition of bile to a neutral or alkaline pancreatic juice causes but little change in its proteolytic action. Some slight stimulation may be produced, but there is no convincing proof that this is of constant occurrence or sufficient in degree to possess much physiological significance. We have been more inclined to the view that while the presence of bile in the intestine may be of primary importance for the assimilation of fats, its action upon trypsin-proteolysis is chiefly negative; *i. e.*, it neither retards nor stimulates proteolysis to any very great degree, under ordinary conditions. Recently, however, another paper[2] bearing on this subject has appeared which renders necessary a reconsideration of this question, for the results which the paper presents are so at variance with the above conclusions and so out of harmony with generally accepted views that some explanation of the apparent divergence must be sought. This is all the more necessary from the fact that comparatively few systematic quantitative experiments have been tried. We have therefore attempted a thorough study of the subject with a view to establishing firmly the nature and extent of the action which bile and its constituents exercise upon pancreatic proteolysis.

In the experiments reported by Rachford and Southgate emphasis is laid upon the fact that they were "planned for the purpose of throwing some light on the proteolytic action of pancreatic juice, under the conditions which normally exist in the duodenum." With this end in view pure pancreatic juice was obtained from rabbits,

[1] Martin and Williams: Proceedings of the Royal Society, 1890. xlviii, p. 160.

[2] Rachford and Southgate: Medical record, 1895, xlviii, p. 878.

through a pancreatic fistula, one rabbit yielding about 1 c.c. of the secretion in from four to six hours, this quantity sufficing for one experiment. As to the character of the bile employed there is no mention. We call attention to these facts because there is a manifest disposition on the part of these writers to accept the results of other workers in this field as conclusive for the pancreatic extracts, etc. employed, while their own divergent results are to be accepted as equally conclusive for the natural pancreatic juice. We are disinclined, however, to admit the correctness of this view. Pancreatic juice owes its proteolytic power to a specific enzyme. If the digestive power of this secretion is modified by the presence of bile through a specific action upon the enzyme it is clear that this influence will be exerted whether we are dealing with the natural secretion or with an extract of the gland. If, however, the influence exerted is an indirect one, affecting the enzyme only through changes of reaction, etc. it is equally manifest that this influence can be detected and measured to the best advantage when the environment is thoroughly known. We see, therefore, no particular advantage in making use of the natural secretion in a study of this kind, especially where the volume available is so small as to render the attainment of accurate quantitative results somewhat difficult. It is true theoretically that the addition of the fresh bile of an animal to the natural pancreatic juice of the same animal may constitute an ideal method for studying the influence of the former upon the activity of the latter; but when the exigencies of the case require that the digestive mixture be made by taking 5 drops of the natural pancreatic juice, adding 60 drops of water and 50 drops of a 4 per cent solution of bile,[1] we see very little reason for believing that the environment is thereby made to approximate any more closely to normal conditions than with the use of artificial extracts of the gland. The point involved is to our minds an important one, aside from the bearing it has upon the question before us. For if it is true that the action of a given agent upon a specific enzyme or upon the specific power of the enzyme, is necessarily different when added to the natural secretion in which the enzyme is contained from that which results when the same agent is added to an extract of the enzyme, then much of our knowledge regarding the conditions modifying and regulating the action of the digestive enzymes is of questionable value.

Rachford and Southgate seemingly incline to the view that the con-

[1] Rachford and Southgate: *loc. cit.*

ditions under which their experiments were carried out approach closely those normally existent in the duodenum. Granting that this may be so, one is still inclined after careful scrutiny of the conditions prevailing in their experiments to wonder what the *actual* conditions really were. Nowhere is there any mention made of the reaction of the fluids employed, nor of the reaction of the resultant mixture when bile, hydrochloric acid, and pancreatic juice were combined. To state merely that a given digestive mixture was prepared by adding 8 drops of pure pancreatic juice, 30 drops of 0.1 per cent hydrochloric acid, and 50 drops of a 4 per cent solution of bile leaves one in great doubt as to whether the mixture so manufactured was acid, alkaline, or neutral, and if acid whether it contained free or only combined acid. These are obviously very important elements to know if definite conclusions are to be drawn in explanation of the results. Data of this sort, however, are wholly wanting in the paper in question, hence we are forced simply to take the results and guess at the actual conditions under which they were obtained. Further, so-called pure pancreatic juice, like the other digestive secretions, is subject to constant modification by the character and extent of the stimulation which calls it forth, while the character and condition of the semi-digested food passing from the stomach into the duodenum, together with the amount of free and combined acid, must necessarily lead to variable conditions in the duodenum. Add to this the well known variations in the rate of flow and composition of the bile, and we may well ask what are the conditions which normally prevail in the duodenum? Obviously, we cannot make a definite answer within very close limits, for the conditions are bound to be more or less variable. What we have to ascertain, therefore, is the influence of bile and its constituents upon the proteolytic action of the pancreatic juice or its specific enzyme under the various conditions which are liable to exist in the upper part of the small intestine. This in our judgment can be studied to the best advantage by the use of artificial pancreatic juice, or extracts of the active gland, where the quantity obtainable will be sufficient to admit of comparative experiments under definite conditions. Moreover, the artificial pancreatic juice will not be widely different in the character of the proteid matter present from the natural secretion employed by Rachford and Southgate. Thus, these investigators state that from four to six hours were required for about one cubic centimetre of the pancreatic juice to flow from the fistula. Plainly, during this interval the active proteolytic enzyme present would transform the natural

proteids of the juice into peptone, amido-acids, etc., as completely as the transformation would be accomplished in the extracts themselves. Hence in this respect, at least, both fluids must differ from the natural secretion normally poured into the intestine.

I. Methods employed.

The pancreatic extracts employed in our experiments were prepared from two kinds of glands and by two distinct methods. 1. Using Kühne's well known method,[1] the fresh pancreatic glands of oxen were freed from fat and thoroughly dehydrated by long soaking in a large volume of strong alcohol and lastly in ether. To prepare the extract, 20 grams of the dry tissue were warmed at 40° C. for 24 hours with 200 c.c. of 0.1 per cent salicylic acid, the solution strained off, filtered through paper, made exactly neutral with sodium carbonate, and diluted with water to 1 litre. The sodium salicylate formed on neutralization will serve to prevent putrefaction for short periods, while the addition of a little thymol will preserve the fluid indefinitely. 2. Using Roberts's method,[2] pancreatic glands from pigs, freed from fat, were ground up with broken glass and soaked in four times their weight of 20 per cent alcohol for 4–5 days with frequent agitation. The extract was then filtered through paper, yielding a clear, slightly yellow fluid of strong proteolytic power.

The proteid material used in measuring the relative proteolytic power of the mixtures was purified blood fibrin, prepared by soaking carefully selected, well-washed fibrin in cold and boiling water until all soluble matter was removed, after which the fibrin was thoroughly extracted with cold and boiling alcohol and lastly with ether. The friable mass was then ground to a coarse powder and the latter passed through a series of sieves so as to bring together particles of the same size. It was then dried at 110° C. until of constant weight, and preserved for use. In some few experiments coagulated egg-albumin was made use of, in which case the actual content of dry proteid was determined by drying a given weight of the coagulum at 110° C. and then determining the ash by ignition.

The character of the bile employed is specified in each experiment. The secretion was always obtained as fresh as possible, and when from dogs or cats it was usually obtained through a temporary biliary fistula.

In arranging the experiments each digestive mixture in a series was

[1] Kühne: Untersuchungen aus d. physiol. Institute, Heidelberg, 1878, I., p. 223.

[2] Roberts: On the digestive ferments, etc., The Lumleian Lectures, London, 1880.

made to contain the same volume of pancreatic juice for each gram of dried fibrin — usually 10 or 20 c.c., according to the strength of the juice — with a total volume of 50 c.c.; water, bile, bile salts, acid, alkali, etc., being added in the proportions necessary to give the percentages specified. All the mixtures of a series were placed in the same water-bath at 40° C., all stirred equally, and when digestive action was sufficiently advanced the undigested residues were collected on weighed filters, previously dried at 110° C. in glass-stoppered weighing bottles, and washed thoroughly with hot water, and lastly with alcohol and ether. On drying the papers with their contents at 110° C. until of constant weight the proportion of undigested matter was readily ascertained, from which the relative proteolytic action of the several mixtures was easily calculated. It is hardly necessary to add that all the mixtures of a given series were kept at 40° C. for the same length of time, usually 2–4 hours, it being our aim to have the proteid material in the control mixture digested to the extent of 40–60 per cent.

II. Influence of Fresh Bile on the Proteolytic Action of the Pancreatic Enzyme in Neutral Solution.

The following quantitative results show the extent and character of the influence exerted by bile from various sources upon neutral solutions of trypsin.

Experiment 1. Pig's bile. Neutral extract of pig's pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.4382 gram	56.18 per cent	100.0
0	0.4477	55.23	98.3
1.0	0.4891	51.09	90.9
3.0	0.4922	50.78	90.3
5.0	0.4616	53.84	95.8
10.0	0.4426	55.74	99.2
15.0	0.4204	57.96	103.1
20.0	0.4052	59.48	105.8
25.0	0.4206	57.94	103.1

Experiment 2. Pig's bile. Neutral extract of pig's pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.4218 gram	57.82 per cent	100.0
0	0.4330	56.70	98.0
1.0	0.4690	53.10	91.8
3.0	0.4705	52.95	91.5
5.0	0.4668	53.32	92.2
10.0	0.4528	54.72	94.6
15.0	0.4172	58.28	100.8

Experiment 3. Pig's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3823 gram	61.77 per cent	100.0
0.25	0.4039	59.61	96.5
0.5	0.4175	58.25	94.3
1.0	0.4948	50.52	81.7
2.5	0.4815	51.85	83.9
5.0	0.5100	49.00	79.3

Experiment 4. Ox bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.2873 gram	71.27 per cent	100.0
1.0	0.3203	67.97	95.3
2.0	0.3203	67.97	95.3
3.0	0.3255	67.45	94.6
5.0	0.3306	66.94	93.9
10.0	0.3323	66.77	93.6
15.0	0.3019	69.81	97.9

Experiment 5. Ox bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.6008 gram	39.92 per cent	100.0
1.0	0.5880	41.20	103.2
2.0	0.6049	39.51	98.9
3.0	0.6157	38.43	96.2
4.0	0.6287	37.13	93.0
5.0	0.6228	37.72	94.4
10.0	0.6179	38.21	95.7

Experiment 6. Dog's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.4070 gram	59.30 per cent	100.0
1.0	0.4165	58.35	98.3
2.0	0.4175	58.25	98.2
3.0	0.4348	56.52	95.3

Experiment 7. Dog's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3353 gram	66.47 per cent	100.0
0.25	0.3389	66.11	99.4
0.5	0.3295	67.05	100.8
1.0	0.3094	69.06	103.8
2.5	0.3579	64.21	96.6
5.0	0.3760	62.40	93.8

Experiment 8. Dog's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.4535 gram	54.65 per cent	100.0
0.25	0.4602	53.98	98.7
0.5	0.4541	54.59	99.8
1.0	0.4461	55.39	101.3
2.5	0.4370	56.30	103.0
5.0	0.4045	59.55	108.9
10.0	0.4188	58.12	106.3
15.0	0.4155	58.45	106.9

Experiment 9. Cat's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.4189 gram	58.11 per cent	100.0
0	0.4226	57.74	99.3
2.0	0.4453	55.47	95.4
7.0	0.4124	58.76	101.1

Experiment 10. Sheep's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.5161 gram	48.39 per cent	100.0
0.25	0.5098	49.02	101.3
0.5	0.5187	48.13	99.4
1.0	0.5271	47.29	97.7
2.5	0.5383	46.17	95.4
5.0	0.5018	49.82	102.9

Experiment 11. Sheep's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.2409 gram	75.91 per cent	100.0
0.25	0.2301	76.99	101.4
0.5	0.2709	72.91	96.0
1.0	0.2645	73.55	96.8
2.5	0.3011	69.89	92.0
5.0	0.3370	66.30	87.3
10.0	0.3142	68.58	90.3

Experiment 12. Sheep's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.4826 gram	51.74 per cent	100.0
0.25	0.4754	52.46	101.3
0.5	0.4717	52.83	102.1
1.0	0.4931	50.69	98.0
2.5	0.4685	53.15	102.7
5.0	0.4689	53.11	102.6
10.0	0.4383	56.17	108.5

Experiment 13. Sheep's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3425 gram	65.75 per cent	100.0
0.5	0.3356	66.44	101.1
1.0	0.3149	68.51	104.2
2.5	0.3258	67.42	102.5
5.0	0.3427	65.73	99.9
10.0	0.3287	67.13	102.0

Experiment 14. Sheep's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.5791 gram	42.09 per cent	100.0
0.25	0.5705	42.95	102.0
0.5	0.5637	43.63	103.6
1.0	0.5635	43.64	103.6
2.5	0.5772	42.28	100.4
10.0	0.5414	45.86	108.9

Experiment 15. Sheep's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3507 gram	64.93 per cent	100.0
1.0	0.3499	65.01	100.1
2.5	0.3492	65.08	101.0
5.0	0.3569	64.31	99.0
10.0	0.3132	68.68	105.7

Experiment 16. Sheep's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3305 gram	66.95 per cent	100.0
0.25	0.3282	67.18	100.3
0.5	0.3243	67.57	101.4
1.0	0.3344	66.56	99.4
2.5	0.3446	65.54	97.8
5.0	0.3398	66.02	98.6
10.0	0.3076	69.24	103.4

Experiment 17. Human bile.[1] Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3042 gram	69.58 per cent	100.0
1.0	0.2980	70.20	100.8
2.0	0.3175	68.25	98.0
3.0	0.3542	64.58	92.8
5.0	0.3652	63.48	91.2
10.0	0.3833	61.67	88.6
20.0	0.4335	56.65	81.4
40.0	0.4305	56.95	81.8

[1] Containing 17.96 per cent of solid matter.

In looking through these various experiments it is manifest that the addition of fresh bile to a neutral pancreatic extract does not give rise to any very great degree of stimulation, *i. e.*, the proteid-digesting power of the enzyme is not markedly increased. Calling the digestive power of the control mixture without bile 100, it is rare to find the digestive power of the enzyme raised above 108 by addition of bile. Increased proteolysis, however, is certainly induced many times by the addition of bile, and it is somewhat noticeable that this increase is obtained more frequently in the presence of large percentages — 10–25 per cent — than in the presence of smaller amounts. Still, in no one of our experiments do we find a confirmation of the results reported by Rachford and Southgate, who found on an average "that the proteolytic action of pancreatic juice on neutral fibrin was increased one-fourth by the addition of bile." Further, it is noticeable in our experiments that in full 50 per cent of the results inhibition of proteolysis is produced, although here, likewise, the retarding effect is not very marked. Rarely does the relative proteolytic action fall below 90. Our results, therefore, seemingly justify the statement that the addition of bile to a neutral solution of the pancreatic enzyme, even to the extent of 25 per cent, does not materially modify its proteolytic power; stimulation or inhibition may result, but not, under ordinary circumstances, to any very great degree. Still, the question arises at once why we have both stimulation and retardation. Obviously, some reason must exist for this apparent discrepancy in the results. First, however, we must call attention to the extent to which our analytical data can be trusted. Many times, to be sure, duplicate results agree very closely, but experience has taught us that, under the conditions of our experiments, the limit of error is about 1 per cent. This means that where 50–60 per cent of proteid matter is digested, relative proteolytic action may vary two points without having any special significance (see Experiments 1, 2, 9, 18, 20, and 30). It is plain, however, on carefully scrutinizing the preceding data, keeping in mind what has just been stated, that in some experiments bile manifestly tends to produce slight inhibition of proteolysis, while in other experiments, apparently under the same conditions, increased proteolysis results. It is further manifest that this difference in action is to be connected mainly with the character of the bile employed. Thus, it is to be noticed that increased proteolysis is much more common with sheep's and dog's bile than with ox or pig's bile. Such differences in action might indeed be expected

when it is remembered how radically bile from different species of animals differs in composition. Still with sheep's bile stimulation of proteolysis is not constant, neither is inhibition always characteristic of pig's bile; but this is not strange when we recall how the bile from a given animal may vary in composition with changes in physiological conditions. Further, as Experiments 1 and 2 indicate, a given sample of bile may when present in one proportion retard proteolysis, while a larger percentage will accelerate digestion. This suggests the possible presence in bile of two opposing factors, one tending to accelerate, the other tending to retard proteolysis. Clearly such action as is produced cannot be due solely to the characteristic bile-salts which are contained in such abundance in the bile.

Bile is usually considered an alkaline-reacting fluid. Thus, Neumeister[1] states that "the reaction of bile is alkaline; it contains about 0.2 per cent sodium carbonate and about the same amount of alkaline-reacting sodium phosphate." It is true that fresh bile usually reacts alkaline to red litmus paper, but we have been unable to find any statements in the literature justifying the assumption that sodium carbonate is present. Indeed, some comparatively recent observations made by Jolles[2] show that the bile of oxen, dogs, and pigs, as well as human bile, reacts acid to phenolphthalein. This obviously does not imply the presence of free acid, although some free fatty acids may be present, such as stearic, palmitic, and oleic acids.[3] Jolles, indeed, concludes from his experiments that the fresh bile of man and the above-mentioned animals is not an alkaline or neutral fluid, but possesses a weak acid reaction. He finds, for example, on titrating ox-bile with a decinormal solution of potassium hydroxide, using phenolphthalein as an indicator, that on an average 1 gram of bile requires 0.546 milligram KOH to neutralize the free acids or acid-salts present. It is to be noted, likewise, that the acidity varies with different samples of bile, the extremes in ten experiments being 0.483 and 0.633. In pig's bile the average acidity was somewhat higher, 0.86 milligram KOH being required to neutralize the acid salts of 1 gram of bile. Further, the variations in acidity were much greater, the extremes in eight observations being 0.56 and 1.56. In dog's bile, on the other hand, the acidity (in one experiment) was only 0.42. Human bile, however, was much more

[1] Neumeister: Lehrbuch d. physiol. Chemie, zweite Auflage, 1897, p. 195.

[2] Jolles, A.: Archiv f. d. ges. Physiol., 1894, lxvii, p. 1.

[3] Lassar-Cohn: Zeitschr. f. physiol. Chemie, 1893, xvii, p. 607.

strongly acid, 1 gram of bile requiring on an average 2.36 milligrams of KOH to neutralize the acid salts. These observations, which have an important bearing upon the subject under consideration, we are able to confirm in a general way through a large number of determinations made in this laboratory [1] upon various kinds of bile. Only in rabbit's bile was there a failure to detect a measurable amount of acidity. Cat's bile, however, showed an acidity equal to only 0.23. Now it is obvious from these statements that bile (excepting possibly rabbit's bile) cannot contain any alkali as strong as sodium carbonate. Such alkaline reaction as bile yields with red litmus, lacmoid, etc., must be due to the presence of such salts as Na_2HPO_4, NaH_2PO_4, etc. We may measure the amount of alkalinity in bile, using lacmoid as an indicator, by titration with a solution of decinormal hydrochloric acid. Using this method, Mr. Brown found on an average that pig's bile having an acidity equal to 0.50 milligram NaOH per gram had an alkalinity equal to 1.05 milligram HCl per gram. Sheep's bile with an average acidity of 0.45 possessed an alkalinity of 0.91. Ox bile with an average acidity of 0.43 showed an average alkalinity of 1.50, while rabbit's bile flowing directly from the liver through a fistula and not coming in contact with the gall bladder had an alkalinity of 2.9 without any measurable acidity. These statements would seem to show that the alkalinity as indicated by lacmoid is considerably greater than the acidity as indicated by phenolphthalein, but this is not always the case, for in some of our experiments, to be quoted shortly, it will be observed that the acidity frequently predominates. We would call special attention, however, to the observation made with rabbit's bile, for if it is true that the latter fluid invariably has a strong alkalinity, the addition of such a bile to neutral pancreatic juice would obviously accelerate proteolysis. If Rachford and Southgate used by chance the bile of the rabbit in their experiments, it might help explain the great acceleration of digestion noticed by them on addition of bile to "neutral fibrin." The point, however, which we wish to emphasize is that the bile of most animals under ordinary conditions is not a strongly alkaline fluid, that it contains no such alkali as sodium carbonate, but on the other hand is possessed of a weak acidity due to the presence of certain acid salts, such as the phosphates of the alkalies, together with possible weak organic acids or other organic compounds. The fact that the acid-reacting bile fails to produce any effect on blue lacmoid is convincing

[1] By Ernest W. Brown, Ph. B.

proof that the fluid does not contain free organic acids of any strength. On the other hand, fresh bile does possess a certain degree of alkalinity to be detected by litmus and lacmoid, but due mainly at least to the presence of salts or compounds which are either acid to phenolphthalein, or which exist side by side with such compounds. Lastly, we would emphasize the fact already brought out, that the so-called acidity of the bile, and likewise the so-called alkalinity, have different values in different species of animals, and may likewise vary in the same species under different conditions of diet, etc.

The bearing of these facts upon the problem before us is sufficiently manifest. The addition of bile to a neutral pancreatic fluid (neutral to litmus) must plainly introduce a change in the reaction, as measured by either litmus, lacmoid, or phenolphthalein. Further, owing to the variations in the acidity and alkalinity, already referred to, it is clear that different samples of bile will produce different results, and when it is remembered how sensitive the proteolytic enzyme trypsin is toward changes of reaction, it is obvious that this feature cannot be overlooked in considering the influence of bile upon pancreatic proteolysis.

Let us consider now the character of the bile used in some of the preceding experiments on proteolysis.

			Degree of Acidity.[1]	*Degree of Alkalinity.*[2]
Experiment	2	Pig's bile	0.50	1.17
"	3	"	0.60	. . .
"	7	Dog's bile	0.90	0.54
"	8	"	0.76	0.40
"	12	Sheep's bile . . .	0.50	0.37
"	13	" . . .	0.40	0.91
"	14	" . . .	0.60	0.73

These data show us at once that in introducing say 10 per cent of bile into the digestive mixtures, variations in reaction must necessarily ensue. Contrast, for example, the bile used in Experiments 2 and 7, also in 12 and 13. Here we have marked differences in the ratio of acid salts to alkaline salts, but without any appreciable difference in the relative proteolytic action of the mixtures. Everything else being equal we should expect to find increased proteolysis most marked in those mixtures where the bile introduced showed a predominance of alkaline salts, but no such conclusion can be drawn from the results. On the

[1] Expressed in milligrams NaOH required to neutralize one gram bile, phenolphthalein as indicator.

[2] Expressed in milligrams HCl required to neutralize one gram bile, lacmoid as indicator.

contrary, it is plain that such slight influence as bile exerts on the proteolytic action of *neutral* pancreatic juice is not connected primarily with change of reaction, but must be attributed to some other cause. These points, however, will be referred to again in another connection.

III. Influence of Fresh Bile on the Proteolytic Action of the Pancreatic Enzyme in Alkaline Solution.

The experiments embraced under this head were conducted in the same manner as those previously described, except that to each digestive mixture was added 0.125 gram of sodium carbonate. Hence, each mixture contained 0.25 per cent sodium carbonate, unless modified by the bile added. Following are the results obtained: —

Experiment 18. Pig's bile. Alkaline extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3721 gram	62.79 per cent	100.0
0	0.3790	62.10	98.9
1.0	0.4440	55.60	88.5
1.0	0.4350	56.50	89.9
2.0	0.4490	55.10	87.7
2.0	0.4699	53.01	84.4
5.0	0.4318	56.82	90.4
5.0	0.4230	57.70	91.8
10.0	0.4255	57.45	91.4
10.0	0.4198	58.02	92.4

Experiment 19. Pig's bile. Alkaline extract of pig's pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3769 gram	62.31 per cent	100.0
1.0	0.3752	62.48	100.2
10.0	0.3997	60.03	96.3
15.0	0.4037	59.63	95.6
25.0	0.4349	56.51	90.6
50.0	0.5048	49.52	79.4

Experiment 20. Pig's bile. Alkaline extract of pig's pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action*
0	0.1535 gram	84.65 per cent	100.0
0	0.1498	85.02	100.4
3.0	0.2080	79.20	93.5
5.0	0.2177	78.23	92.4
10.0	0.2462	75.38	89.0
15.0	0.2400	76.00	89.7
20.0	0.2603	73.97	87.3
25.0	0.2428	75.72	89.4
30.0	0.2560	74.40	87.8
40.0	0.2743	72.57	85.7

Experiment 21. Pig's bile. Alkaline extract of ox pancreas.[1]

Per cent of Bile.	*Undigested residue.*	*Albumin digested.*	*Relative proteolytic action.*
0	0.0891 gram	88.41 per cent	100.0
0	0.0832	89.20	100.8
2.0	0.1320	82.80	93.6
5.0	0.0765	90.07	101.8
15.0	0.0257	96.66	109.3
20.0	0.0262	96.47	109.1

Experiment 22. Ox bile. Alkaline extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.2482 gram	75.18 per cent	100.0
1.0	0.2565	74.35	98.8
2.0	0.2771	72.29	96.1
3.0	0.2929	70.71	94.0
4.0	0.2860	71.40	94.9
5.0	0.2862	71.38	94.9
10.0	0.3036	69.64	92.6
15.0	0.2827	71.73	95.4

Experiment 23. Calf's bile. Alkaline extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.2996 gram	70.04 per cent	100.0
1.0	0.3190	68.10	97.2
2.0	0.3409	65.91	94.1
3.0	0.3348	66.52	94.9
4.0	0.3314	66.86	95.4
5.0	0.3113	68.87	98.3
10.0	0.2662	73.38	104.6
15.0	0.2750	72.50	103.5

Experiment 24. Human bile.[2] Alkaline extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.2960 gram	70.40 per cent	100.0
0.5	0.3080	69.20	98.2
1.0	0.3091	69.09	98.1
2.0	0.3085	69.15	98.2
3.0	0.3074	69.26	98.3
5.0	0.3267	67.33	95.6
10.0	0.3360	66.40	94.3
20.0	0.3980	60.20	85.5
40.0	0.4904	50.96	72.3

[1] In this experiment, thoroughly washed coagulated egg-albumin was employed instead of blood fibrin. Each mixture contained originally 3 grams of the coagulum = 0.7707 gram of dry proteid.

[2] Containing 13.3 per cent of solid matter.

Experiment 25. Dog's bile. Alkaline extract of pig's pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.1598 gram	84.02 per cent	100.0
0	0.1779	82.21	97.8
0.5	0.1855	81.45	96.9
1.0	0.2237	77.63	92.3
5.0	0.2041	79.59	94.7
10.0	0.2433	75.67	90.0
15.0	0.2481	75.19	89.4

Experiment 26. Dog's bile. Alkaline extract of pig's pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.1884 gram	81.16 per cent	100.0
2.0	0.1513	84.87	104.5
4.0	0.1148	88.52	109.0
8.0	0.1470	85.30	105.1
15.0	0.1894	81.06	99.8

Experiment 27. Dog's bile. Alkaline extract of pig's pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3913 gram	60.87 per cent	100.0
5.0	0.3593	64.07	105.2
10.0	0.3622	63.78	104.6

Experiment 28. Dog's bile. Alkaline extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.5374 gram	46.26 per cent	100.0
20.0	0.5267	47.33	102.3

Experiment 29. Sheep's bile. Alkaline extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3935 gram	60.65 per cent	100.0
0.25	0.3880	61.20	100.9
0.5	0.4079	59.21	97.6
2.5	0.4236	57.64	95.3
5.0	0.4135	58.65	96.7
10.0	0.4002	59.98	98.8

Experiment 30. Sheep's bile. Alkaline extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3284 gram	67.16 per cent	100.0
0	0.3330	66.70	99.3
0.25	0.3293	67.07	99.8
0.5	0.3328	66.72	99.3
1.0	0.3151	68.49	101.9
2.5	0.2937	70.63	105.1
5.0	0.2913	70.87	105.5
10.0	0.2635	73.65	109.6
15.0	0.2419	75.81	112.8

On looking through these results and comparing them with those of the preceding series, it is apparent that the addition of bile to an *alkaline* pancreatic juice is liable to produce a greater relative retardation of proteolysis than the addition of the same amount to a *neutral* pancreatic fluid. An alkaline pancreatic juice, however, containing even 40 per cent of bile will digest as much proteid in a given time as the same pancreatic fluid neutralized but without the addition of bile. If the control mixtures of the two series are compared, it will be observed that the alkaline fluids dissolve on an average about 10–15 per cent more proteid than the neutral fluids. This is merely an illustration of the well-known fact that a weak alkaline fluid is much more favorable for pancreatic proteolysis than a neutral fluid. We are inclined to attribute such retardation of proteolysis as bile induces when added to an alkaline pancreatic fluid in great part to the reduction of alkalinity liable to occur. We say liable because this will depend primarily upon the relative proportion of acid and alkaline salts in the bile. When the latter contains a relatively large proportion of acid salts, as indicated by phenolphthalein, the addition of large percentages of such a bile will rapidly diminish the amount of sodium carbonate present, since the latter will be more or less used up in transforming the acid compounds into neutral ones. This is well illustrated in Experiment 20, wherein actual examination showed that at the conclusion of the digestion all the mixtures containing more than 15 per cent of bile had lost entirely their alkaline reaction toward litmus. In other words, the acid-reacting compounds contained in 10 grams of this bile were sufficient to neutralize the 0.125 gram of sodium carbonate originally present in the mixture. In harmony with this fact it is to be noted throughout these latter experiments that retardation is most marked in the presence of those biles which have been shown to have as a rule the highest acidity, viz., pig's bile and human bile. With dog's bile, on the other hand, in which acidity is usually very slight, no retardation whatever was observed; all three experiments gave evidence of some slight stimulation of proteolysis. The occasional stimulation noticed with sheep's bile and pig's bile we attribute in part to the lower acidity of the samples used. Leaving these points out of consideration, however, and turning our attention to the collected data, it is plain that the addition of even 40 or 50 per cent of bile to an alkaline pancreatic fluid does not greatly retard the proteolytic action of the enzyme (see Experiments 19, 21, and 24), certainly no more than would result from neutralization of the alka-

linity. By this we do not mean that the specific bile salts are without influence on pancreatic proteolysis, but merely that the changes in reaction resulting from addition of normal bile are in themselves sufficient to account for the retardation noticed. Similarly, such stimulation of proteolysis as results may be due as much to a more favorable change in the reaction of the mixture as to any other cause.

IV. Influence of Bile Salts on the Proteolytic Action of the Pancreatic Enzyme in Neutral and Alkaline Solution.

In considering the action of the salts of the bile acids on pancreatic proteolysis it is to be remembered that in ox bile both glycocholate and taurocholate of sodium are present, although the proportion of the two acids is subject to considerable variation. In most cases, when ox bile is acidified, the proportion of taurocholic acid present is sufficient to hold the less soluble glycocholic acid in solution, but in some cases the latter predominates to such an extent that it will crystallize out under the above conditions. Thus Marshall[1] found as the result of an examination of 543 samples of bile from as many oxen that a separation of glycocholic acid could be obtained in only 121 cases, *i. e.*, in 22.2 per cent. This fact is worthy of note in the present connection as illustrating not only the variable composition of bile from a given species, but also as an indication of the variability of composition to be expected in the preparation of "crystallized bile."[2] Further, in pig's bile we have to do mainly with the sodium salts of two special forms of glycocholic acid known as α- and β- hyo-glycocholic acid.[3] In the preparation of crystallized bile, *i. e.*, the sodium salts of the above acids, the ordinary methods of procedure were followed, and need not be detailed here.

Following are the results obtained in studying the influence of these preparations on pancreatic proteolysis under the conditions specified.

[1] Marshall, J.: Zeitschr. f. physiol. Chemie, 1887, ii. p. 233.

[2] For the variation in the proportion of glycocholate and taurocholate present in human bile see the results reported by Hammarsten: Zur Kenntniss der Lebergalle des Menschen. Mitgetheilt der königl. Gesellsch. d. Wissenschaften zu Upsala, 15 Juni, 1893. Separatabzug.

[3] Jolin, S.: Zeitschr. f. physiol. Chemie, 1888, xii. p. 512, and xiii. p. 205.

Experiment 31. Crystallized ox-bile salts. Neutral extract of ox pancreas.

Per cent of Bile salts.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.2933 gram	70.67 per cent	100.0
0	0.2707	72.93	103.1
1.0	0.2819	71.81	101.6
2.0	0.2579	74.21	105.0
3.0	0.3144	68.56	97.0
5.0	0.3790	62.10	87.8

Experiment 32. Crystallized ox-bile salts. Neutral extract of ox pancreas.

Per cent of Bile salts.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.3866 gram	61.34 per cent	100.0
0.25	0.4481	55.19	89.9
1.00	0.4675	53.25	86.8
2.00	0.4651	53.49	87.2
3.00	0.4528	54.72	89.2
5.00	0.4360	56.40	91.9

Experiment 33. Crystallized ox-bile salts. Alkaline[1] extract of ox pancreas.

Per cent of Bile salts.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.4940 gram	50.60 per cent	100.0
0	0.4970	50.30	99.4
1.0	0.4729	52.71	104.1
2.0	0.4465	55.35	109.3
3.0	0.4722	52.78	104.3

Experiment 34. Pure crystallized sodium glycocholate. Alkaline extract of ox pancreas.

Per cent of Glycocholate.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.5374 gram	46.20 per cent	100.0
0	0.5277	47.23	102.2
1.0	0.5459	45.41	98.3
2.0	0.5573	44.27	95.8
3.0	0.5987	40.13	86.8

Experiment 35. Bile salts from pig's bile. Neutral extract of pig's pancreas.

Per cent of Bile salts.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.5781 gram	42.19 per cent	100.0
0.5	0.6197	38.03	90.1
1.0	0.6427	35.73	84.6
2.0	0.6894	31.06	73.6
3.0	0.7105	28.95	68.6

Experiment 36. Bile salts from pig's bile. Alkaline extract of pig's pancreas.

Per cent of Bile salts.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.4935 gram	50.65 per cent	100.0
0.5	0.4989	50.11	98.9
1.0	0.4750	52.50	103.6
2.0	0.4709	52.91	104.4
3.0	0.5383	46.17	91.1

[1] Each mixture containing 0.25 per cent sodium carbonate.

The contrast between the results obtained in the two preceding experiments led to our testing the reaction of the bile salts prepared from pig's bile, and it was found that they were quite strongly acid to litmus. It is thus evident that the marked inhibition of proteolysis observed in Experiment 35 was due, in part at least, to the increasing acidity of the mixtures. In Experiment 36, on the other hand, the 0.125 gram of sodium carbonate present overcame this acidity except in the mixture containing 3.0 per cent of the bile salts.

Experiment 37. Bile salts from pig's bile. Alkaline extract of pig's pancreas. These bile salts were exceedingly acid, hence 0.25 gram Na_2CO_3 was added to each mixture, thus making the amount of this salt 0.5 per cent in the control. In the presence of 3.0 per cent of the bile salts, however, the alkalinity was reduced to one-fifth.

Per cent of Bile salts.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.1752 gram	82.48 per cent	100.0
0.5	0.2045	79.55	96.4
1.0	0.2142	78.58	95.2
2.0	0.2282	77.18	93.5
3.0	0.3281	67.19	81.4

Experiment 38. Bile salts from pig's bile, made neutral before addition. Alkaline extract of pig's pancreas. Each mixture containing 0.25 per cent Na_2CO_3, as usual.

Per cent of Bile salts.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.1846 gram	81.54 per cent	100.0
0.5	0.2249	77.51	95.0
1.0	0.2207	77.93	95.5
2.0	0.2222	77.78	95.3
3.0	0.2324	76.76	94.1
5.0	0.2543	74.57	91.4

Experiment 39. Bile salts from pig's bile, made neutral before addition. Extract of ox pancreas.

Character of the Fluid.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral + 0 Bile salts	0.5499 gram	45.01 per cent	100.0
" + 1.0% "	0.6467	35.33	78.4
" + 3.0% "	0.6966	30.34	67.4
" + 5.0% "	0.7701	22.99	51.0
0.25 % Na_2CO_3 + 0 Bile salts . .	0.2748	72.52	161.1
" " + 1.0% " . .	0.3992	60.08	133.4
" " + 3.0% " . .	0.5238	47.62	105.7
" " + 5.0% " . .	0.6750	32.50	72.2

A critical examination of the foregoing results shows us first that the bile salts from ox bile have no very great influence in either direction upon pancreatic proteolysis. In two experiments (31 and

33) there is some evidence of acceleration, while in one experiment retardation is more noticeable. With pure sodium glycocholate (3 per cent) relative proteolytic action is reduced from 100 to 87. In Experiment 47, to be quoted later, stimulation of proteolysis is quite marked. In considering these results, however, in their bearing on the influence of fresh bile, it is to be remembered that 3–5 per cent of these bile salts are equivalent to the addition of 40–50 per cent of the original bile. With regard to the apparent difference in action of the several samples of ox bile salts we are inclined to attribute this to variations in the proportion of glycocholate and taurocholate present. Pure glycocholate, other influences excluded, seems to have a greater inhibitory action than the mixed salts, and possibly the more pronounced retardation seemingly characteristic of the salts from pig's bile is due to the fact that the salts are mainly glycocholates. Still it is to be observed that the samples of salts from pig's bile vary considerably in the intensity of their action, and this independently of their acidity, for when the latter is neutralized the same retarding effect is still produced. Somewhat noticeable also is the difference in intensity of action of the neutralized bile salts (from pig's bile) when added to the pancreatic juice of the same species as contrasted with the result obtained when the salts are added to the pancreatic extract from another species (contrast Experiments 38 and 39). The results collectively certainly warrant the conclusion that the isolated bile salts taken by themselves do not exert any very marked stimulation of pancreatic proteolysis. They may, on the other hand, give rise to some retardation, — an effect which is seemingly more characteristic of the salts from pig's bile than of those common to ox bile. It is to be noted, however, that the salts from pig's bile were not so pure chemically as the crystallized salts separated from ox bile, but frequently showed an acid reaction.

The above somewhat unsatisfactory results have served to strengthen our conviction that such limited action as normal bile exerts on pancreatic proteolysis is the result mainly of influence on the reaction of the digestive mixture, and that many agencies other than the specific bile salts are concerned. No doubt, some of these are more or less antagonistic to each other. Thus, pig's bile, as has been frequently stated by many observers, is liable to be extremely viscid, but the viscidity is not always conspicuous; at times the bile is quite limpid. This viscidity is due, in great part at least, to a mucin or nucleoal-

bumin, precipitable by alcohol, and we have found that when this substance is removed from the bile there is a noticeable difference in the influence of the fluid on proteolysis. We may cite the following experiment:

Fresh pig's bile, very viscid, having a specific gravity of 1036, an acidity of 0.58, and an alkalinity of 1.15, was treated with five volumes of strong alcohol, the precipitate filtered off, and washed with alcohol. The united filtrate and washings were then evaporated for the removal of the alcohol, and the fluid made up with distilled water to the original volume. The acidity was now 0.48, and the alkalinity 0.90. The action of a portion of the original fresh bile and of the bile freed from nucleoalbumin, etc., on proteolysis was then tested.

Experiment 40. With fresh pig's bile. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.5777 gram	42.23 per cent	100.0
0.25	0.6088	39.12	92.6
0.50	0.6241	37.59	89.0
1.00	0.7000	30.00	71.0
2.50	0.7118	28.82	68.2
5.00	0.6496	35.04	82.9
10.00	0.7235	27.65	65.4

Experiment 41. With bile freed from nucleoalbumin. Neutral extract of ox pancreas.

Per cent of Bile.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.6446 gram	35.54 per cent	100.0
0.25	0.6556	34.44	96.9
0.50	0.6651	33.49	94.2
1.00	0.7007	29.93	84.2
2.50	0.7351	26.49	74.5
5.00	0.7217	27.83	78.3
10.00	0.6598	34.02	95.7

It is noticeable from these two experiments that the removal of the nucleoalbumin, with possibly some of the inorganic salts from pig's bile, diminishes in a general way the retarding effect of the latter on proteolysis. Somewhat noticeable also is the peculiar relationship in the rise and fall of proteolysis under the influence of different percentages of the two samples.

With ox bile an attempt was made to separate the fluid into three distinct fractions, using methods which would presumably cause little or no change in the nature or composition of the various constituents. For this purpose 440 c.c. of fresh ox bile, containing 12.4 per cent of solid matter, were evaporated to a very thick syrup on the water-bath and precipitated with absolute alcohol. The small precipitate which

resulted was filtered off, washed thoroughly with alcohol, and then dried over sulphuric acid. It weighed 2.27 grams. The alcoholic filtrate was treated with a large volume of ether, the precipitated bile salts filtered off, washed thoroughly with ether, and dried. The alcohol-ether filtrate was allowed to evaporate, and finally brought to complete dryness on the water-bath. The effect of these three fractions on pancreatic proteolysis was then determined in the usual manner. The bile salts and the residue from the alcohol-ether filtrate were readily soluble in water, but the alcoholic precipitate was not completely soluble. Following are the results obtained: —

Experiment 42. With a neutral extract of ox pancreas.

Per cent of Bile Constituents.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.4217 gram	57.83 per cent	100.0
0.5 Bile salts	0.4533	54.67	94.5
1.0 "	0.4452	55.48	95.9
1.5 "	0.4415	55.85	96.5
0.25 Alcoholic p.p.	0.3862	61.38	106.1
0.5 " "	0.3704	62.96	108.8
1.0 " "	0.4059	59.41	102.7
0.5 Alcohol-ether filtrate	0.4147	58.53	101.2
1.0 " "	0.4032	59.68	103.2
1.5 " "	0.3759	62.41	107.9

Experiment 43. A duplicate of the preceding, except that an alkaline (0.25 per cent Na_2CO_3) extract of ox pancreas was employed.

Per cent of Bile Constituents.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
0	0.1886 gram	81.14 per cent	100.0
0.5 Bile salts	0.2847	71.53	88.1
1.0 "	0.2883	71.17	87.7
1.5 "	0.2655	73.45	90.5
0.25 Alcoholic p.p.	0.2388	76.12	93.8
0.5 " "	0.2345	76.55	94.3
1.0 " "	0.2370	76.30	94.0
0.5 Alcohol-ether filtrate	0.2473	75.27	92.7
1.0 " "	0.2929	70.71	87.1
1.5 " "	0.2689	73.11	90.1

From the first of these two experiments, where a neutral pancreatic fluid was employed, it is seen that the fraction containing the bile salts produces a slight inhibition of proteolysis, while the other two fractions increase the proteolytic action of the enzyme. Also noticeable is the tendency of the material from the alcohol-ether filtrate to increase proteolysis in proportion to the amount added, while the favorable action of the alcoholic precipitate appears to diminish with

increase in the proportion used. That these peculiarities of action, however, are not due to any direct influence upon the proteolytic enzyme is evident from the fact that in the second experiment where the reaction of the digestive mixtures is alkaline these differences disappear. The bile salts still produce inhibition, but the other two fractions no longer give rise to increased proteolysis; on the contrary, they tend to check the rate of proteolysis. It is thus clearly evident that in bile there are present various elements capable under different conditions of producing divergent effects, in minor degree, upon pancreatic proteolysis — effects which may counterbalance each other to some extent.

V. Influence of Bile and Bile Salts on the Proteolytic Action of the Pancreatic Enzyme in the Presence of Free and Combined Acids.

It has been generally accepted, on the basis of what has seemed sufficient experimental evidence, that the proteolytic enzyme of the pancreas is practically inactive in the presence of free hydrochloric acid.[1] Even *free organic* acids inhibit almost completely the action of the enzyme. Further, the presence of combined acid, *i. e.*, combined with proteid matter, checks to a greater or less degree the activity of the digestive fluid. Rachford and Southgate, however, state: "in our experiment we have found that the proteolytic action of pancreatic juice on fibrin is quite as strong in a one-thirtieth per cent hydrochloric-acid solution as it is in a neutral solution. If there is any difference, in fact, it is in favor of the hydrochloric-acid solution." The statement is positive, but we cannot find in their paper any *conclusive* evidence as to the actual degree of acidity. Thus, to quote one of their experiments, 10 minims of pure pancreatic juice, 50 minims of water, and 30 minims of 0.1 per cent hydrochloric acid were mixed together; — but how much of this acid was used in neutralizing the alkalinity of the pancreatic juice, and how much was combined with the proteids of the secretion? Nowhere in their paper can we find any evidence of discrimination between free and combined acid, or any attempt to determine the actual percentage of either free or combined acid really present. The question is one of considerable physiological importance, and if it is true that the pancreatic juice acting in an

[1] Chittenden and Cummins: Studies in physiol. chemistry. Yale Univer. 1885, vol. i, p. 135. This paper contains full references to other work in this direction.

acid solution will do more work than in a neutral solution, it should be clearly established. We have, therefore, first turned our attention to this point.

Experiment 44. With neutral extracts of ox pancreas and pig's pancreas (neutral to litmus).

10 c.c. of the extract of pig's pancreas required 4.95 c.c. 0.2 per cent HCl to combine with all the proteid matter present.[1]

10 c.c. of the extract of ox pancreas required 2.55 c.c. 0.2 per cent HCl to combine with the proteids.

In the digestions with pig's pancreatic fluid each mixture contained 10 c.c. of the extract, while with the pancreatic fluid from the ox pancreas 30 c.c. of extract were used in each case. Acid was then added to the mixtures as specified, the percentages being calculated on the total volume (50 c.c.) of the digestive mixtures. In no case was any *free* acid present.

Ox pancreatic juice.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral	0.3279 gram	67.211 per cent	100.0
Proteids combined with HCl —			
Quarter saturated (0.007% HCl)	0.3782	62.18	92.5
Half " (0.015% ")	0.4995	50.05	74.4
Wholly " (0.03% ")	0.8710	12.90	19.1
Pig's pancreatic juice.			
Neutral	0.0435	95.65	100.0
Proteids combined with HCl —			
One-sixth saturated (0.0016% HCl),	0.0469	95.31	99.6
Quarter " (0.0025% "),	0.0550	94.50	98.7
Half " (0.0049% "),	0.0826	91.74	95.9
Wholly " (0.0099% "),	0.2239	77.61	81.1

Experiment 45. 10 c.c. of the extract of ox pancreas required 4.3 c.c. 0.2 per cent HCl to combine with the proteids.

10 c.c. of the extract of pig's pancreas required 4.6 c.c. 0.2 per cent HCl to combine with the proteids.

In the digestions, 10 c.c. of the extract of pig's pancreas, and 30 c.c. of the extract of ox pancreas were employed.

Ox pancreatic juice.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral	0.3896 gram	61.04 per cent	100.0
Proteids combined with acid —			
One-eighth saturated (0.006% HCl),	0.3951	60.49	99.0
One-sixth " (0.008% "),	0.4798	52.02	85.2
One-fourth " (0.012% "),	0.5030	49.70	81.4
One-half " (0.025% "),	0.6509	34.91	57.1
Wholly " (0.05% "),	0.9327	6.73	11.0

[1] Tropæolin oo in methyl alcohol was used as the indicator for free acid. Obviously, in conducting the titrations, deduction was made for the excess of acid required to bring out the color.

Pig's pancreatic juice.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral	0.1966 gram.	80.34 per cent.	100.0
Proteids combined with acid—			
One-sixth saturated (0.003% HCl),	0.2110	78.90	98.2
One-fourth " (0.004% "),	0.2654	73.46	91.4
One-half " (0.009% "),	0.3281	67.19	83.6
Wholly " (0.018% "),	0.5564	44.36	55.2

Experiment 46. With extract of ox pancreas. 25 c.c. of the neutral extract required 19.7 c.c. 0.4 per cent *salicylic acid* to combine with the proteids present.

Character of the fluid.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral	0.4658 gram	53.42 per cent	100.0
"	0.4894	51.06	95.5
Proteids combined with acid—			
Completely saturated (0.157% acid),	0.9860	1.40	2.6
" " "	0.9874	1.26	2.3
Half " (0.078% acid),	0.8443	15.57	29.1
" " "	0.8375	16.25	30.4

In considering the results of the three preceding experiments it is to be remembered that in no one of the digestive mixtures was there any *free* acid present, hence such effects as are produced come solely from the influence of the combined acid. Of the latter, even a few thousandths of one per cent suffice to exert an inhibitory influence on proteolysis, and with a sufficient amount of combined acid alone, even with a weak organic acid, proteolysis may be almost completely checked. We fail to see therefore how the addition of acid to a *neutral* pancreatic juice can increase the digestive power of the solution.

What now is the influence of bile and bile salts on pancreatic proteolysis in the presence of combined acid? The answer to this question is found in the results of the following experiments.

Experiment 47. With extract ox pancreas. Ox-bile salts.

Character of the fluid.	*Undigested residue.*	*Fibrin digested*	*Relative proteolytic action.*
Neutral	0.5291 gram	47.09 per cent	100.0
" + 2% Bile salts	0.5183	48.17	102.3
" + 4% "	0.4818	51.82	110.0
Proteids combined with acid—			
Eighth saturated " (0.005% HCl) .	0.5860	41.40	87.9
" " " + 2% Bile salts .	0.5589	44.11	93.6
Quarter " " (0.01% HCl) .	0.6330	36.70	77.8
" " " + 2% Bile salts .	0.6359	36.41	77.3
" " " + 4% " .	0.6230	37.70	80.0

Experiment 48. With extract of pig's pancreas. Bile salts from pig's bile.

Character of the fluid.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral	0.1755 gram	82.45 per cent	100.0
Proteids combined with HCl —			
Half saturated " (0.013% HCl) .	0.2337	76.63	92.9
" " " + 0.5% Bile salts.	0.4433	55.67	67.5
" " " + 1.0% "	0.4039	59.61	72.2
" " " + 2.0% "	0.4958	50.42	61.1
" " " + 3.0% "	0.4992	50.08	60.7

Experiment 49. With extract of pig's pancreas. Bile salts from pig's bile. The salts somewhat acid in reaction. Salicylic acid used to combine with the proteids.

Character of the fluid.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral	0.3041 gram	69.59 per cent	100.0
" + 3% Bile salts	0.5338	46.62	66.9
Proteids combined with acid —			
Wholly saturated " (0.064%) . .	0.5795	42.05	60.4
" " " + 3% Bile salts.	0.7608	23.92	34.3
Half " " (0.032%) . .	0.4296	57.04	81.9
" " " + 3% Bile salts.	0.6773	32.27	46.3
Quarter " " (0.016%) . .	0.3608	63.92	91.8
" " " + 3% Bile salts.	0.5591	44.09	63.3

Experiment 50. With extract of pig's pancreas. Bile salts from pig's bile made perfectly neutral. Salicylic acid used to combine with the proteids.

Character of the fluid.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral	0.2132 gram	78.68 per cent	100.0
Proteids combined with acid —			
Half saturated " (0.053% acid) .	0.6038	39.62	50.3
" " " + 0.5% Bile salts.	0.7659	23.41	29.7
" " " + 1.0% " .	0.8120	18.80	22.6
" " " + 2.0% " .	0.8319	16.81	21.3
" " " + 3.0% " .	0.8900	11.00	13.9

Experiment 51. With extract of ox pancreas. Fresh pig's bile. Salicylic acid used to combine with the proteids.

Character of the fluid.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral	0.4125 gram	58.75 per cent	100.0
Proteids combined with acid —			
Half saturated " (0.038% acid) .	0.7111	28.89	49.1
" " " + 0.5% Bile . .	0.7242	27.58	46.9
" " " + 1.0% " . .	0.7283	27.17	46.2
" " " + 5.0% " . .	0.7662	23.38	39.7
" " " + 10.0% " . .	0.7854	21.46	36.5
" " " + 20.0% " . .	0.7819	21.81	37.1

Experiment 52. Neutral extract of ox pancreas. Fresh ox bile.

In this experiment the proteids of the pancreatic extract were not treated with acid, but sufficient acid was added to the fibrin to saturate it, or half saturate it (as tested by tropæolin oo), prior to addition of the pancreatic extract.

Conditions.	*Undigested residue.*	*Fibrin digested.*	*Relative proteolytic action.*
Neutral Fibrin	0.3643 gram	63.57 per cent	100.0
Fibrin saturated with acid (5 c.c. 0.2% HCl),	0.5755	42.45	68.3
" " " + 10% Bile . . .	0.5490	45.10	70.9
" half " " (2.5 c.c. 0.2% HCl),	0.4690	53.10	83.5
" " " " + 5% Bile . . .	0.4980	50.20	78.9

In only one of these experiments (Experiment 47) do we see any distinct suggestion of aid to pancreatic proteolysis when bile or bile salts are added to a pancreatic extract containing combined acid. Combined acid alone tends to retard proteolysis, and the addition of bile to such mixtures as a rule increases still further the extent of retardation. Our results afford no confirmation whatever of the view that bile greatly aids pancreatic juice in its proteolytic action on acid fibrin. Neither are we inclined to believe "that pancreatic juice, plus bile, plus hydrochloric acid, can accomplish more work in proteolysis than can any other known pancreatic mixture."[1] If such were the case we fail to see why some evidence of such favorable action should not appear in our results. The inhibitory action of acids alone, and of acids and bile combined, on pancreatic proteolysis is not in our judgment to be looked upon as unfavorable to the normal digestive processes of the small intestine. What right have we to assume that the conditions existent in the normal duodenum are such as to require pancreatic proteolysis to take place in the presence of acid, either free or combined? The combined or free acid which passes from the stomach through the pylorus is without doubt quickly removed by absorption or destroyed by neutralization. The evidence is certainly in favor of the view that the contents of the duodenum are generally alkaline. This question has been admirably discussed in a recent paper by Moore and Rockwood,[2] in which also a large number of experimental data are offered, showing that in many animals at least, under different forms of diet, the contents of the intestine from pylorus to cæcum react alkaline. In some cases, to be sure, the contents closely adjacent to the pylorus were

[1] RACHFORD and SOUTHGATE: *loc. cit.*

[2] MOORE and ROCKWOOD: Journal of physiology, 1897, xxi, p. 373.

found to be acid, but when this was the case the acidity was usually limited to a few inches. Hence, we are inclined to believe that pancreatic proteolysis as it occurs in the normal intestine takes place, to a great extent, in the presence of a neutral or alkaline reaction, and that under such conditions the proportion of bile ordinarily present is not inimical to the process.

THE REINFORCEMENT OF VOLUNTARY MUSCULAR CONTRACTIONS.

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IN 1890 Bowditch and Warren[1] found that the knee-jerk was accelerated or reinforced when the interval between the various sensory stimuli used in their experiments and the blow on the patellar tendon was less than three-tenths second; when this interval exceeded three-tenths second an inhibitory or negative result was obtained. Their results were so uniform that it seemed desirable to ascertain whether sensory stimuli would exert a similar influence upon voluntary muscular contractions, and to that end the following experiments were undertaken.

The subject of the experiment contracted his muscles rhythmically every three seconds. The signal for contraction was the sound of a metronome beating every half second. The contractions were recorded by means of Mosso's ergograph and were registered on a revolving drum. Each contraction was communicated by the recording lever of the ergograph to a Czermak electric double lever. The reader may be reminded that this most useful piece of mechanism (Fig. 1) was designed to record the limits of oscillation of a moving body without being otherwise affected by the movements of the body. By it an electric current can be either made or broken at the moment when the movement has reached its full extent. It consists of two levers (C) and (I) (Fig. 2), each connected with one pole of a battery (F). Both levers move on the same axis (H). The first lever (C) is U-shaped and freely movable. It embraces the second lever. The latter (I) is stationary, except

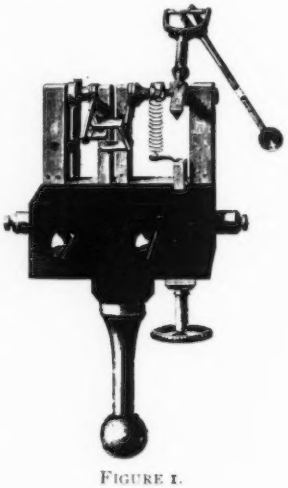

FIGURE 1.

[1] BOWDITCH and WARREN: Journal of physiology, 1890, xi, p. 25.

when either elevated or depressed by the action of the first. Each arm of the first lever can be made either a conductor or a nonconductor by means of small screws (B and C), tipped with platinum or ivory respectively. This lever is connected with the ergograph (K) at L. A movement of the recording arm (A) of the ergograph (K), which is connected with the long or "U" lever (C) at L, brings one of the arms of the "U" into contact with the indifferent, *i. e.*, stationary lever I. Should this be the arm carrying the ivory-pointed screw no connection is made, but if it be the arm with the platinum-pointed screw the current is at once completed. By means of this instrument and an automatic short-circuiting key (E), which it was subsequently found necessary to introduce, the stimuli were controlled in a definite manner. Thus, when A was depressed or in a position of rest, *i. e.*, the position it occupied when the muscles were completely relaxed, C was raised, through its connection at L, and made to turn on the axis at H, and so to pull on the cord (J) attached to the key E and hence to short-circuit itself automatically. Without this arrangement unavoidable vibrations would have broken the circuit through the sensitive contact of a and b and thus have caused the signal marker (B) and the electro-magnet (G) to act. With this arrangement, however, when A began to ascend, C was lowered and contact made between a and b, while the spring at E pulled open the short-circuiting key, the cord J between C and E being relaxed, and so allowed the current to pass a—b; consequently the ivory-tipped screw c—by elevating C and so drawing b away from a—broke the circuit

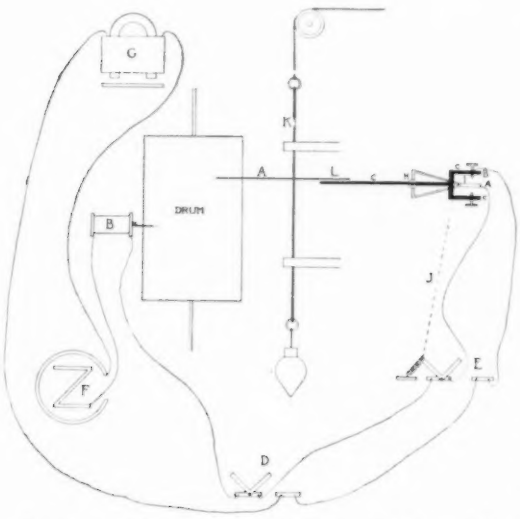

FIGURE 2. Diagram of the double-lever and the recording apparatus.

as soon as the recording lever (A) of the ergograph (K) began to descend.[1]

The stimuli used in these experiments were light flashed into the eye, a sudden sound, and induction shocks applied to the skin. For the retinal stimulus a flash from a thirty-two candle-power electric lamp was suddenly brought to bear on the eyes, which were in darkness, by means of Czermak's lever, the subject at the beginning of his muscular contraction breaking the current[2] and so by means of the electro-magnet (G) releasing a catch which let fall the shutter of the box containing the electric lamp. The sound stimulus was effected in the same way, except that the breaking of the circuit released a hammer which struck upon a tin disk connected with the ears by a stethoscope. Similarly, in the case of the stimulation of the skin, the breaking of the circuit opened the short-circuiting key in the secondary circuit of a du Bois-Reymond inductorium, hammer in action, and so let a series of induction shocks pass to the subject through common sponge electrodes fastened to the left arm (the right made the contractions). The point at which the reinforcing stimuli were made was indicated on the drum by an electric signal marker. The subject usually contracted against the weight of two kilogrammes. The electric current was under the immediate control of the operator, by means of the short-circuiting key (D), which cut out the action of Czermak's lever and the automatic key (E); consequently no stimulus could take place except at the will of the operator, for the circuit could not be broken by Czermak's lever unless D was open. The operator closed the circuit at irregularly varying intervals so that the subject might not know when the stimulus was to be applied. Fig. 2 illustrates the electrical connections for the three stimuli of sound, light, and the induction shock.

It was found that a sensory stimulus applied just as the muscle was beginning to contract, caused an increase in the height of the contraction (Fig. 3).

At this point in the research Hofbauer[3] published experiments similar to my own. He used sound as the reinforcing stimulus and

[1] For a full account of the double lever see CZERMAK, J. H.: Der electrische Doppelhebel, Leipzig, 1871.

[2] The contact screws of Czermak's lever were here reversed, the lower one (c) being the conductor; the previous description applies to the arrangement in the experiments to be described presently.

[3] HOFBAUER: Archiv f. d. ges. Physiol., 1897, lxviii, p. 546.

obtained practically the same results. In both researches the augmentation was particularly noticeable as fatigue set in and the contractions grew smaller.

The most important feature noticed in my experiments was the fact that the relaxation following a stimulated contraction was de-

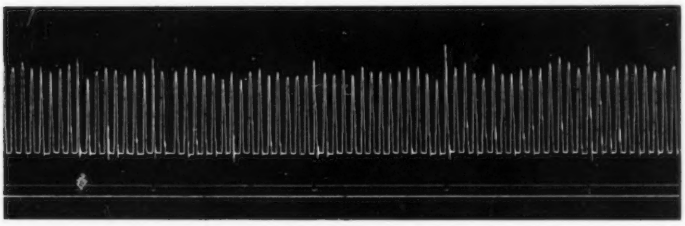

FIGURE 3. One fourth original size. Reinforcement of voluntary contraction by sensory stimuli. The sensory stimulus was applied at the breaks in the horizontal line beneath the contractions. The load was one kilo.

cidedly quicker and more complete than that following a normal or unstimulated one, even when the stimulated contraction showed no signs of augmentation, and as Hofbauer's paper fully covered the ground of the augmented contractions, attention was now turned to the relaxation phenomena. Czermak's levers were now so arranged that the reinforcing stimulus should be made at the moment the subject began to relax from a contraction.[1] With this arrangement it was found that the duration of relaxation is very considerably shortened when the subject is stimulated at the moment of relaxation, as the accompanying tracings show. So marked was this phenomenon that whereas the average time of a whole unstimulated or normal muscle-curve was about one second, the time of a contraction reinforced at the moment of relaxation averaged only 0.65 second, the difference (0.35 second) being taken from the time of relaxation. The stimulated relaxation is not only quicker than the normal but also more complete; the end of a normal relaxation is slow; usually it exhibits one or two very long curves before reaching the base line, which it approaches in a very gradual manner. Relaxation under the influence of the stimulus, on the contrary, shows nothing of this, but is

[1] The contact screw was changed from c to b, c being now the non-conductor; thus electric contact was preserved during the contraction period but broken as soon as relaxation began. See the description of the apparatus and its connections on page 337.

a sudden sharp drop directly to the base line and sometimes beyond it. Fig. 4 shows this clearly, the broken-line curve being the stimulated one.

In the course of the research it was noticed that the relaxation of some of the subjects was quicker than that of others, while the height of their normal contraction varied also, some persons giving a strong, high contraction while others gave a small, feeble one. Again, some reacted in a more decisive way than others, and in a few instances the subject gradually became accustomed to the stimuli and reacted more slowly than at first. In some cases, finally, it was observed that the next contraction following the reinforced one exhibited the same phenomenon (see Fig. 5), but this occurred in a manner too irregular to enable conclusions to be drawn from it.

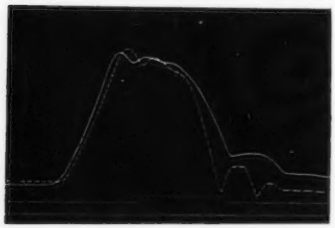

FIGURE 4. One-fifth original size. The curves record voluntary muscular contractions (load, one kilo). In the broken curve, during the period marked by the rise in the line just above the time record, a faradic current was applied to the skin. The breaks in this curve were painted in after the curve was drawn. The lowest tracing gives the time in fifths of seconds.

The table on page 341 shows at a glance the effect of the various stimuli on muscular relaxation.

Each of the three parts of the table is compiled from one tracing, in each case taken from a different individual, and is typical of the results obtained from all the other tracings. The same number of normal and stimulated contractions are given in order to facilitate comparison. In the first section of the table light was the reinforcing stimulus; it was applied at the beginning of muscular *relaxation*. From this portion we can see that in a normal muscular movement the period of muscular relaxation is slightly longer (equal in two cases) than the time of contraction, while in the movements with simultaneous retinal stimulation the reverse is the case, the time of relaxation being considerably shorter than the time of contraction (see Fig. 3). With sound as the stimulus, the same results are noticed, the shortening of the relaxation time being again marked. The same effect is gained by a simple cutaneous sensory stimulus (electric). No attempt was made to find the results of using powerful shocks.

The duration (in seconds) of voluntary muscular contraction and relaxation (1) without simultaneous stimulation, and (2) with simultaneous visual, auditory, or cutaneous stimuli at the beginning of relaxation.

Light.				Sound.				Induction shocks to the skin.			
No stimulus.		Stimulus at beginning of relaxation.		No stimulus.		Stimulus at beginning of relaxation.		No stimulus.		Stimulus at beginning of relaxation.	
Contraction.	Relaxation.	Contraction.	Relaxation.	Contraction.	Relaxation.	Contraction.	Relaxation.	Contraction.	Relaxation.	Contraction.	Relaxation.
.5	.7	.45	.35	.4	.5	.4	.2	.4	.5	.4	.4
.5	.5	.55	.2	.4	.5	.4	.3	.4	.5	.45	.3
.5	.6	.45	.35	.5	.5	.6	.4	.4	.55	.35	.35
.5	.7	.5	.3	.35	.45	.5	.25	.3	.6	.5	.3
.55	.55	.5	.25	.5	.5	.45	.3	.4	.4	.5	.3
.51	.61	.49	.29	.43	.49	.47	.29	.38	.51	.44	.33
——AVERAGES——											

It appears, therefore, that the phase of relaxation after voluntary muscular contraction is shortened by a sensory stimulus applied at the beginning of relaxation.

I pass now to a discussion of the cause of this interesting phenomenon. It is necessary to inquire first whether the shortening of the relaxation phase (or acceleration of relaxation) is due to a reflex contraction of the extensors of the forearm, now relaxing from their contraction as antagonists during the contraction of the flexor muscles. Such a reflex contraction of the extensors would forcibly elongate the relaxing flexors and thus shorten their phase of relaxation.

The solution of this new problem required that the contractions of both extensors and flexors should be registered simultaneously, — a difficult task, as it proved, necessitating an addition to the apparatus already in use. The wrist being fixed as before in Mosso's ergograph, the subject flexed his arm so as to bring the upper arm at right angles to the forearm. Two upright supports firmly screwed to the base board of the ergograph embraced the elbow and upper arm, which were then tightly bandaged in this position, the bandage including the uprights and the upper arm so that no portion of the

limb except the finger in connection with the ergograph could move. The button of a Marey receiving tambour was placed in contact with the integument over the extensors, the tambour itself being supported from below. Connection was now made with a recording tambour, the lever of which carried a Pflüger's marker which wrote vertically on the drum; this did away with the difference that would result were one curve drawn by a lever moving perpendicularly and the other (extensor) curve drawn by a lever which moved in the arc of a circle.

Over twenty different subjects were examined, and rather more than five hundred contractions were taken from each. The tracings obtained by this method all showed the same characteristics and demonstrated the fact that the antagonistic extensors and the flexors relax in the same way. In other words, the stimulus seemed to affect

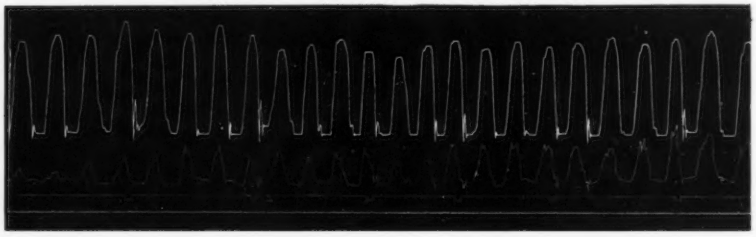

FIGURE 5. One-fourth original size. The uppermost curve was drawn by the flexors of the forearm. The second curve was drawn by the extensors. The breaks in the third curve indicate the stimuli. The lowermost curve is the time in fifths seconds.

the extensors in a similar manner to the flexors. Figure 5 shows the action of both sets of muscles under the influence of the reinforcing stimulus of sound. The tracing is especially valuable as the subject was contracting against the weight of only one kilo, thus minimizing any influence which the weight might have on the relaxation of the muscles. In this tracing the points of the recording levers were accurately placed in the same vertical line. It is seen from these results that the acceleration of the relaxation phase cannot be explained by the reflex contraction of the extensors of the forearm.

A second explanation suggests itself. The relaxation phase in voluntary contraction may perhaps be regarded as the gradual subsidence of the contraction-discharge from the motor neurons. If such a process were inhibited by the stimulation of the retina, the auditory

apparatus, or the skin, the flexor muscles would at once cease to oppose the extending force exerted by the load which they had raised. The passive muscles would then be rapidly extended by the load, and the relaxation curve would fall more steeply, as actually observed. Instances of the reflex inhibition of motor discharges in consequence of sensory excitation are sufficiently numerous. The interesting experiment of Bubnoff and Heidenhain [1] may be cited as an example. These observers found that in some stages of morphine poisoning the subminimal electrical excitation of a cortical motor field produces strong tonic contractions lasting for some time. If a sensory stimulus, such as gently stroking the skin, or blowing on the face, is now applied, the muscles at once relax. The contraction process in the central neurons is in this case cut short by the sensory stimulus. Attractive as this explanation of the acceleration of relaxation witnessed in my experiments may be, there are reasons which seem to preclude its acceptance. An examination of Fig. 5 will show that a muscle weighted with one kilo relaxed as quickly as one weighted with three kilos. Had the contraction process been suddenly inhibited, the extension of the still partially shortened flexors — now no longer in receipt of the motor discharge from the central neurons — would have been more rapid with the greater load. In my experiments, an increase in the load was not followed by an increase in the rapidity of relaxation.

If the quickening of relaxation is not to be explained by the contraction of antagonists or by the passive extension of the muscles in consequence of the reflex inhibition of the contraction process in the phase of sinking energy, — and these explanations cannot be reconciled with my results, — there seems to be no way of avoiding the conclusion that the quickening is due to the augmentation of an active relaxation process. That the phase of sinking energy in the contraction process is as much an active conversion of stored power as is the phase of rising energy has been long considered probable. Indeed, instances are not wanting of a modification of the contraction process by the stimulation of peripheral nerves. Richet [2] and Biedermann [3] have thus relaxed the contracted muscles of a crayfish claw and the

[1] Bubnoff and Heidenhain: Archiv f. d. ges. Physiologie, 1881, xxvi, p. 137.

[2] Richet: Cong. période internat. d. sc. méd. Compt. rend., 1879. Amst.: 1880, vi, p. 554–560.

[3] Biedermann: Sitzungsber. der königl. Acad. der Wissensch. zu Wien, 1887, xcv, p. 7.

sartorius muscle of a dog to which veratrine had been given. Kaiser[1] tetanized the nerve of a muscle that had been brought into a state of tonic contraction by exciting its nerves with glycerine, and observed relaxation. Wedensky[2] finds that an ordinary nerve muscle preparation may be made either to relax or to contract according to the strength of the stimulus employed. Many other instances could be cited. Further, we possess ample evidence that cerebral influences may directly cause relaxation in muscular tissue. A familiar example is the action of the inhibitory fibres of the vagus on the heart. Muscular relaxation has even been obtained by direct cortical stimulation. Thus Bubnoff and Heidenhain[3] found that stimulation of the motor fields of contracted muscles, and indeed of other fields as well, would produce relaxation. Sherrington and Hering[4] have also obtained muscular relaxation by stimulating cortical motor areas. It is with these experiments that my own results should probably be placed, for they show that in the human subject sensory stimuli modify reflexly the relaxation from voluntary muscular contraction as well as the contraction itself.

The result of my experiments, then, favors the view that the acceleration of relaxation is due to the augmentation of an "active" relaxation process, rather than to the inhibition of the contraction process, but it would perhaps, in the present state of knowledge, be unsafe to make too positive a statement regarding the nature of the phase of sinking energy in muscular contraction.

In conclusion I desire to express my appreciation of the many valuable suggestions of Professor Bowditch, under whose direction this work was done.

Summary.

1. A sensory stimulus applied at the beginning of a voluntary contraction increases the height of the contraction.

2. The relaxation following a contraction with intercalated sensory stimulus is quicker and more complete than when no stimulus is given.

3. This acceleration of relaxation is not due to augmentation of the contraction of the antagonistic muscles, for the relaxation of the ex-

[1] Kaiser: Zeitschrift für Biologie, 1891, xxviii, p. 423.

[2] Wedensky: Archives de physiologie, 1891, iii, p. 687.

[3] Bubnoff and Heidenhain: *loc. cit.*

[4] Sherrington and Hering: Archiv f. d. ges. Physiol., 1897, lxviii, p. 222.

tensors does not visibly differ in rapidity and extent from the relaxation of the flexor muscles.

4. The acceleration of relaxation cannot be ascribed to the sensory stimulus inhibiting the discharge from the motor neurons and thus permitting the rapid passive extension of the muscles by the load of the ergograph, for the acceleration does not increase with the increase of the load.

5. In the present state of knowledge, the acceleration is best explained as an augmentation of an active relaxation process by the sensory stimulus.

ON CERTAIN CHARACTERISTICS OF THE PRESSURE SENSATIONS OF THE HUMAN SKIN.

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BY pressure sensations are to be understood those sensations which are provoked by non-painful mechanical stimuli applied to the skin. It appears that such stimuli must produce a local deformation of the skin in order to be effective. In Meissner's experiment of immersing the hand in mercury of the temperature of the skin, a considerable amount of pressure is exerted upon the skin of the submerged part, but no sensations are there provoked. In this case there is sufficient pressure to stimulate, but, a large surface being subjected to the same pressure, there is no deformation and consequently no sensation.

Von Frey [1] has shown that mechanical stimuli of threshold strength are felt only at the moment of their application, the continuation and end of the stimulus not being perceived; that is, the sensation vanishes very soon after the application of the weight, and the removal of the weight is not noticed. He has shown, further, that stimuli above the threshold strength may be felt as continuing sensations, although the intensity of the sensation diminishes, the unloading being always more difficult to perceive than the loading. The sensation may outlast the stimulus, probably as a result of the deformation of the skin, which remains for some time. Finally, von Frey has demonstrated that the effectiveness of the stimulus depends upon certain factors in addition to the strength of the stimulus; namely, upon the size and position of the surface stimulated and the rapidity with which the stimulus is applied.

In order to determine more clearly the value of the physiological factors involved, von Frey devised test hairs (Reizhaare), which furnish a very circumscribed mechanical stimulus, capable of gradation, and thus measure quite accurately the number, position, and relative

[1] von FREY: Abhandl. d. math.-physikal. Cl. d. königl. Sächsischen Gesellsch. d. Wissensch., 1896, xxiii, p. 175.

sensitiveness of the points designated by Blix [1] as "pressure points." These "test hairs" consist of short pieces of hair, preferably from the human head, glued by one end at right angles to the end of a small stick. For each hair two measurements are made; a micrometer measurement of the diameter of the cross-section, from which the area of the cross-section is calculated; and the weight which the hair can lift when its free end is brought to bear on a scalebeam. The later measurement determines the "power" of the hair. It has been found that approximately the maximal power can be obtained without undue bending of the hair, and further, that the area of the cross-section and the power remain quite constant for long periods of time. The "pressure" of the hair is its power per unit of surface, that is, the quotient of its power divided by the area of its cross-section. Variety in the sectional surface of the different hairs used and variety in the power of different hairs of the same sectional surface can be obtained by taking pieces of hair of different length.

By means of the test hairs it is found that the sensations of pressure are provoked only at certain so-called "pressure points" which are constant in their location but which vary in the number distributed to equal areas of skin. The pressure points are therefore separated by intervals which are not sensitive to this form of stimulus, and these intervals increase in size as the sensitive points are more scattered. The pressure points are fatigued by rapidly repeated stimuli, but soon regain their normal sensitiveness when left to themselves. Upon the haired portion of the skin, estimated to amount to about 95 per cent of the whole, it has been found that the pressure points correspond to the number of the hairs, the point being located over the hair sac not far from the spot where the hair pierces the epidermis; — the hairs as a rule grow obliquely out of the skin. Such pressure points are subject to stimulation by movements of the hairs — which act as levers — as well as by the deformation produced by the direct contact of objects with the surface of the skin.

With such small surfaces as those of the test hairs it has been observed that physiological effectiveness is not proportional to the amount of pressure used. Test hairs of greater surface and power are more effective than those of smaller surface and less power notwithstanding their hydrostatic pressure may be the same. Test hairs, the power of which is proportional not to the surface of the applied end, but to the radius of that surface, are found to be of equal physi-

[1] Blix: Zeitschrift für Biologie, 1884, xx, p. 141.

ological value. From this it is assumed that the organs thus stimulated are not superficial in their location but lie somewhat deeper, the effect of the deformation upon the deeper lying structures being more marked when the surface over which the pressure is applied is increased. With larger surfaces than those of the test hairs the deformation always attains its maximum effect at the deeper levels of the skin, and then the physiological effectiveness of the deformation-producing stimulus becomes proportional to its pressure.

During the summer of 1897 I had the opportunity of co-operating with Professor von Frey in the Physiological Institute of the University of Leipzig in some extension of the investigations along the line on which he has been engaged, and I gratefully acknowledge my indebtedness to him.[1] The first object of the research thus jointly undertaken was to determine whether deformation caused by traction (Zug), — which is opposite in direction to that produced by pressure (Druck), — excites the same organs that have been shown to be called into action by pressure, or whether the skin contains also organs which react to traction. It is evident that external objects in contact with the skin produce chiefly the deformations of pressure rather than those of traction, but a brief consideration will show that the tissues of the skin may be subject to pressure, or to changes of pressure, by movements of the underlying structures of the motor apparatus, and that the terminal organs of the so-called pressure sense may be thereby excited. The skin presents a very uneven surface, here convex, there concave, as it conforms to the varying contour of the bones and muscles over which it is stretched. A change of position of these structures must necessarily change the natural tissue-pressure in the overlying skin, increasing that of convex areas when their convexity is increased, and diminishing it when their convexity is diminished: increasing that of concave areas when their concavity is decreased and diminishing it when their concavity is increased. Variations in pressure corresponding to those caused by the deformation of local traction as well as that of local pressure from external objects, but due to body movements, may therefore play a rôle in exciting the nerve organs of the skin, and the impulses thus provoked may be assumed to contribute to our knowledge of the position and the condition of a part, a function ascribed by some to "common sensibility."

[1] The chief results of our observations have been briefly reported by von Frey to the königliche Sächsische Gesellschaft der Wissenschaften in Leipzig (Berichte, Aug. 2, 1897).

Our observations were directed to very small and to large surfaces on the left wrist and thumb, and to the effects of momentary and continued stimuli of different degrees of intensity. The results are given first for very small surfaces, then for large surfaces.

Very Small Surfaces. — The method of investigation was as follows: — The pressure points on the triangular non-haired area at the distal end of the anterior surface of the left forearm (which we may term for the sake of brevity the left wrist) were very carefully sought out by the aid of suitable test hairs. Each point was then marked with a minute drop of silver nitrate solution. The physiological character of the surface to be stimulated was thus determined so far as the pressure sense is concerned, and the stimulus could be applied as desired directly to the chosen sensitive point or points, or, as the pressure points in this particular locality are widely scattered, to a non-sensitive area. In order to ensure fixation of the surface to be tested and at the same time the comfort of the person upon whom the tests were to be made (the "Reagent," as we shall term him), the left forearm was held in a plaster of Paris form moulded to fit the forearm from the elbow to the tips of the fingers, leaving its anterior surface exposed sufficiently to allow the forearm to be drawn out and inserted at will. The stimuli were applied by means of a double-arm thin wooden lever 20 or 30 centimetres in length, the axis of which was supported by a heavy and practically immovable stand. The arms of the lever being of unequal length, the lever was brought into equilibrium by a rider placed upon the shorter and remote arm. A light straw attached at right angles to the end of the longer arm served to transmit its movements to the surface of the skin to which the stimulus was to be applied. The surface of the free end of the light straw, the area of which was 0.3 mm.^{2} to 0.5 mm.^{2}, was glued to the skin, various kinds of adhesive substances being used (Le Page's "Liquid Glue," Collodion, etc.). Weighting the longer arm of the lever — that towards the skin — served to produce pressure; weighting the shorter arm served, on account of the adhesion of the straw, to produce traction. Disturbing oscillations of the lever, and the consequent rapidly changing deformations of the skin, when the weights were brought to bear upon one or the other of the arms of the lever, were avoided by suspending the weights by rubber bands tied to the lever arms. Sometimes two equal weights were suspended at the same time from each arm of the lever at equal distances from its axis, the lever being

thus left in equilibrium, and one weight was allowed to produce its effect by quickly raising the other with the hand. During the tests care was taken to avoid all external disturbance, and the Reagent sat with closed eyes in the most comfortable position possible, attentive to the locality of the skin to be stimulated. The word "now" warned him when a stimulus was about to be applied, and the attention was then especially concentrated.

Two protocols of such tests follow, one having been made upon an isolated sensitive pressure point, the other between previously located points upon a surface not sensitive to pressure: —

June 4, 1897. **Reagent C.** End of straw glued upon a sensitive pressure point on the volar side of the left wrist. Surface loaded: 0.3 mm².

Time. h.	Time. m.	Actual weight in grams.	Reply of Reagent to Stimulus of: Pressure.	Reply of Reagent to Stimulus of: Traction.
12	28	10	Pressure (after 20 sec.) weaker; (after 30 sec.) vanished.	
	30	4	. . . . .	Pressure, stronger than before; remains.
	42	2	. . . . .	Nothing.
....		4	. . . . .	Traction?
	54	10	Pressure, continuing, not strong; after 30 sec., vanished.	
....		2	. . . . .	Touch, vanishes very quickly.
	57	10	Touch, weak, only momentary.	
....		4	. . . . .	Pressure, rather strong, soon diminishing, after 20 sec. apparently gone, then again perceived, finally definitely vanished.
1	1	4	. . . . .	Touch, very weak; after a few seconds, gone.
....		10	Touch (better sensation of deformation), stronger than before, lasting longer (about 20 sec.).	
....		4	. . . . .	Touch, continues some seconds.
....		10	Traction, probably; after 20 sec., gone.	
....		6	. . . . .	Pressure? Not strong.

June 5, 1897. **Reagent C.** End of straw glued upon a space between three pressure points on the volar side of the left wrist. Surface loaded: 0.3 mm².

Time. h. m.	Actual weight in grams.	Reply of Reagent to a Stimulus of	
		Pressure.	Traction.
11 51	2	Touch, momentary but distinct.	
....	2	. . . . .	Touch, the same strength but lasting longer.
54	10	Pressure, distinct and lasting; after 20 sec., weaker; after 35 sec., uncertain; after 50 sec., nothing.	
....	2	. . . . .	Touch, momentary pressure.
12 00	2	Touch, momentary.	
....	4	. . . . .	Touch, momentary, weaker than before.
....	2	Touch, momentary, somewhat more distinct.	
....	2	. . . . .	Touch, pressure distinct but momentary.
....	10	Touch, distinct and lasting; after 10 sec., weaker; after 20 sec., vanished.	
....	....	. . . . .	Touch, very momentary and somewhat weak.
24	2	. . . . .	Touch, momentary; after 30 sec., gone.
....	2	Touch, momentary, but as strong as before.	
....	5	. . . . .	Pressure, continuing, but not long; after a few seconds, gone.

From the foregoing and other similar tests it was found that the so-called pressure points shown to be sensitive to the deformation caused by pressure are equally sensitive to the deformation caused by traction, and, what is most striking, it was seen that with very small surfaces there is inability to determine the direction of the deformation, that is, to distinguish between pressure and traction, the sensation being that simply of a deformation even with strengths of stimulus which are very marked and the action of which is long continued. Pressure and traction each produced comparatively quick fatigue, the duration of the sensation falling markedly

short of that of the stimulus, and the removal of the stimulus being unperceived.

Attention was next turned to the determination of the effect of fatigue produced by a long continued pressure stimulus upon momentary traction stimuli following immediately after the removal of the fatiguing load. The stimulus used to produce fatigue consisted of a 400 gram weight hung upon the pulley of the axis of the lever. The distance of the weight from the axis was $\frac{1}{40}$ that between the axis and the straw by which the load was transmitted to the skin. Thus the actual weight upon the tested surface was 10 grams. The sectional area of the end of the straw being 0.5 mm.^{2}, the actual pressure was 20 grams to the square millimetre. The momentary stimuli were obtained by means of small double-arm thin wooden levers arranged at right angles to the main lever already described and so placed that they could be made to strike upon it on each side of and at equal distances (*e. g.*, about $\frac{1}{10}$ the lever length) from its axis. These levers were moved by weights hung upon the pulley of the axis on the side towards the main lever, and the height of their stroke was determined by an adjustable screw in a post placed under the remote arm of each lever to serve as a stop. This arrangement permitted the selection of a stroke that could provoke a weak or a distinct sensation as desired; and, by depressing the remote arm till it touched the stop and then suddenly releasing it, any number of uniform momentary stimuli could be applied.

An isolated, sensitive pressure point was selected and the end of the straw glued upon it. The following protocols set forth the results obtained from two series of tests in which momentary stimuli of pressure and then of traction were applied, the fatigue in both cases being caused by pressure.

The results of such tests as those here given in detail show that with very small surfaces repeated momentary pressure or traction stimuli of a uniform strength just above the threshold value always excite a similar sensation, if the pause between successive stimuli is sufficient to avoid fatigue. The results show also that if a strong pressure-producing stimulus be allowed to act sufficiently long to produce fatigue and then removed and momentary rhythmical stimuli immediately applied, the latter are not at first perceived, but soon begin to be felt, although imperfectly, and with an increasing distinctness inconstant in degree. Several minutes may elapse before the

sensations regain their original uniform strength. It was shown further that the fatigue produced by pressure is as effective in im-

July 3, 1897. **Reagent C**. End of straw glued upon a very sensitive pressure point on the radial side of the left wrist. Surface loaded: 0.5 mm². Fatiguing stimulus 20 grams mm². Momentary or "stroke" stimuli as near threshold strength as possible.

A. — Momentary or stroke stimulus applied as a pressure stimulus.

Time. h.	m.	sec.	Stimulus.	Statements of Reagent.
			Stroke stimulus applied several times.	Felt each time, but weak.
11	3	00	Fatiguing stimulus applied.	
		30	. . . . .	Weaker.
	4	00	. . . . .	Uncertain.
		30	. . . . .	Nothing.
	6	00	Fatiguing stimulus removed.	Nothing.
			Stroke stimulus applied.	No.
	6	15	. . . . .	Uncertain.
		30	. . . . .	No.
		45	. . . . .	No.
	7	00	. . . . .	Yes, very weak.
		15	. . . . .	Uncertain.
		30	. . . . .	Yes, weak.
		45	. . . . .	Uncertain.
	8	00	. . . . .	Yes, weak.
		15	. . . . .	Yes, weak.
		30	. . . . .	No.
		45	. . . . .	No.
	9	00	. . . . .	Yes, weak.
		15	. . . . .	No.
		30	. . . . .	Yes.
		45	. . . . .	Yes, very weak.
	10	00	. . . . .	Yes.
		15	. . . . .	Yes.
		30	. . . . .	Uncertain.
		45	. . . . .	Yes, weak.
	11	00	. . . . .	Yes.
		15	. . . . .	Yes, it becomes more distinct.
		30	. . . . .	Yes.
		45	. . . . .	Yes.
	12	00	. . . . .	Yes, quite constant and distinct.

July 3, 1897. **Reagent C.** — *Continued.*

B. — Momentary or stroke stimulus applied as a traction stimulus.

Time. h.	m.	sec.	Stimulus.	Statements of Reagent.
			Stroke stimulus applied several times.	Felt each time, weak but distinct, about as strong as pressure stimulus in A.
11	28	00	Fatiguing stimulus applied.	
	29	30	. . . . .	Not completely vanished.
	30	30	. . . . .	Uncertain, variable.
	31	00	Fatiguing stimulus removed.	Nothing.
			Stroke stimulus applied.	Uncertain.
		15	. . . . .	No.
		30	. . . . .	No.
		45	. . . . .	Uncertain.
	32	00	. . . . .	No.
		15	. . . . .	No.
		30	. . . . .	No.
		45	. . . . .	Uncertain.
	33	00	. . . . .	Yes, but very weak.
		15	. . . . .	Yes, a little more distinct.
		30	. . . . .	Very weak.
		45	. . . . .	Yes.
	34	00	. . . . .	Yes, still weak.
		15	. . . . .	Uncertain.
		30	. . . . .	Yes.
		45	. . . . .	No.
	35	00	. . . . .	Yes.
		15	. . . . .	Yes.
		30	. . . . .	Yes.
		45	. . . . .	Uncertain.
	36	00	. . . . .	No.
		15	. . . . .	No.
		30	. . . . .	Yes.
		45	. . . . .	Yes.
	37	00	. . . . .	Yes.
		15	. . . . .	Yes.
		30	. . . . .	Yes.
		45	. . . . .	Yes.
	38	00	. . . . .	Yes.

pairing the sensations provoked by subsequent momentary traction stimuli as those called out by pressure stimuli of the same strength. Therefore the pressure which causes fatigue for pressure also causes an equal fatigue for traction.

Large Surfaces. — It has been shown thus far that with very small surfaces points most sensitive to pressure are also most sensitive to traction; that their sensitiveness to each kind of stimulus is approximately the same; that fatigue produced by pressure is fatigue for subsequent traction stimuli as well as for pressure stimuli; and that even with strong and continued stimuli producing deformation in one or the other direction there is inability to determine the direction of the stimulus, that is, to distinguish between pressure and traction. Tests were now made upon larger surfaces. A cork disc with a sectional area of 50 mm.^{2} was slipped on to the free end of the straw used in the foregoing tests and glued upon the surface to be tested. Observations were first made to determine the effect of momentary stimuli applied to the skin upon the most convex part of the ball of the left thumb. Such stimuli were obtained by the "stroke levers" arranged as in the foregoing tests and could be changed at will from pressure to traction. These observations were followed by others with continued stimuli of different strengths.

Following is a protocol: —

July 7, 1897. **Reagent F.** End of cork glued on the convex surface of the ball of the left thumb. Surface loaded: 50 mm^2. Very strong **momentary stimuli** by "stroke levers."

Time. h. m.	Kind of Stimulus.	Statements of Reagent.	Time.	Kind of Stimulus.	Statements of Reagents.
11 25	Pressure.	Yes.	Intervals 5 to 10 sec.	Pressure.	Yes.
Intervals 5 to 10 sec.	Traction.	Yes, the same.		Traction.	Strong.
	Traction.	Yes.		Pressure.	Strong.
	Pressure.	Yes.		Traction.	Strong.
	Pressure.	Weak.		Pressure.	Perhaps weaker.
	Traction.	Strong.		Traction.	Strong.
Pressure and traction not distinguished.					

Continued stimuli Instead of "stroke levers," weights were hung on main lever four-tenths of its length distant from its axis. Duration of stimulus from 5 to 10 seconds, with intervals of several seconds.

With 100 grams.			
With 100 grams acting as pressure or traction according to the pleasure of the observer and without previous information to the person upon whom the observations were made, 10 such stimuli were each correctly judged as to the direction of the stimulus.			
With 20 grams.			
Kind of Stimulus.	Statements of Reagent.	Kind of Stimulus.	Statements of Reagent.
Pressure.	Uncertain.	Traction.	Traction.
Traction.	Perhaps traction.	Pressure.	Traction, uncertain.
Traction.	Perhaps traction.	Pressure.	Also traction.
Pressure.	Pressure.	Traction.	Also traction.
Pressure.	Uncertain.	. . . .	. . . . .

Repeated tests of the above character made on both of us upon the wrist as well as upon the thumb and with stimuli of different strengths, showed that with large surfaces momentary stimuli of pressure and traction even of marked strength, provoking distinct sensations, could not be distinguished as to their direction, a deformation undetermined in character being in each case alone perceived. When stimuli were continued instead of momentary it was found that with smaller weights, that is, with a diminution in the strength of the stimuli, the ability to judge of the character of the deformation was also impaired.

In order to obtain equality in the rapidity of application of the continued stimuli and thus eliminate the influence of that factor, which had previously been shown to be an important one in the effectiveness of pressure stimuli, the following arrangement of the apparatus already described was made. The weights hanging on rubber bands attached to each side of the axis of the main lever were supported by the two levers previously used as "stroke levers" but now placed under the main lever. The ends of the arms that supported the weights rested upon a shelf attached to a horizontal clock-work kymograph drum. Rotation of the drum carried the ends of the levers down and

allowed the weights which they supported to act upon the main lever. By placing a sufficiently heavy rider upon the remote arm of either lever that lever could be held in place so that only one weight would be brought to act upon the main lever when the drum was set in motion. The excursion of the drum was limited to about one-fourth revolution. The stimulus was removed by turning the drum back by the hand to its former position, the shelf lifting the end of the lever and thereby the weight. A counterpoise clamped on the opposite side of the drum served to offset the effect of the weights upon the shelf when the drum was at rest and a stimulus was not being applied. In the above manner a continued pressure or traction stimulus of any desired strength could always be applied with the same rapidity.

A protocol of a test made under such conditions is presented below. The tests showed clearly that a certain degree of strength is essential to a correct judgment of the kind of deformation produced by continued stimuli upon large surfaces. By gradually increasing the strength of stimulus, the size of the surface stimulated and the rapidity of application of the stimulus remaining constant, it was found that the ability to distinguish the direction of the deformation appeared with a certain increase of weight, not suddenly but gradually, some still undetermined difference in the character of the stimulus being first noticed. With stimuli of sufficient strength a correct judgment as to their direction could always be formed: —

July 16, 1897. **Reagent F** End of cork glued upon the convex surface of the ball of the left thumb. Surface loaded: 10 mm². Continued stimuli 30 grams, two-tenths lever length from axis of main lever, corresponding to an actual load of 6 grams. Duration of stimulus, 10 seconds.

Time. h.	m.	Kind of Stimulus.	Statements of Reagent.
10	37	Pressure.	Distinct excitation, continuing; not determinable whether pressure or traction, perhaps traction.
	41	Traction.	The same, but weaker, lasting a very short time.
	45	Traction.	More distinct, does not last very long; believe it is pressure. More distinct than second stimulus, about as long as first.
	50	Pressure.	Distinct, lasting; different from the preceding excitation, perhaps traction.
	55	Pressure.	Distinct and lasting; cannot say what it is.
11	00	Traction.	Weaker, very weak, almost momentary.

30 grams, pressure side 2 spaces from axis; actual load 6 grams.
30 grams, traction side 2½ spaces from axis; actual load 7.5 grams.

Time. h. m.	Kind of Stimulus.	Statements of Reagent.
11 15	Traction.	Quite distinct, not very strong, impossible to distinguish.
18	Pressure.	Distinct, lasting; not determinable whether pressure or traction, perhaps traction.
22	Pressure.	Distinct, lasting, gradually vanishing; perhaps pressure, quite uncertain.
27	Traction.	Distinct, lasting; not determinable.
31	Traction.	Yes, distinct and lasting; perhaps pressure.
34	Pressure.	Exactly the same as to intensity and character.
All stimuli notably of equal strength. (It is to be noted that the removal of the stimulus was not perceived, and that the sensation outlasted the stimulus.)		

Conclusions.

Collectively the tests show that the recognition of the direction of a deformation, that is, the ability to distinguish between pressure and traction, depends upon the size of the surface stimulated, the duration of the stimulus, and the strength of the stimulus. The perception of a deformation is therefore a simpler psychological process than the recognition of its character. The impulses provoked by variations in pressure appear to contain in themselves no determination of the direction of the exciting deformation. That determination is gained by a combination of impulses of some intensity, of more than momentary duration, and arising from a not too limited area of the skin.

Our demonstration that the points most sensitive to pressure are equally sensitive to traction; that the impulses produced by stimuli in either direction provoke simply sensations of deformation without indications as to its direction; that a stimulus which causes fatigue for pressure stimuli causes also fatigue for traction stimuli; and that the strength of the stimulus, the rapidity of its application, and the size and the location of the surface to which it is applied, influence equally the effectiveness of traction and of pressure stimuli — makes it probable that the organs in the skin which are stimulated by pressure are also stimulated by traction.

THE MOVEMENTS OF THE STOMACH STUDIED BY MEANS OF THE RÖNTGEN RAYS.[1]

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[*From the Laboratory of Physiology in the Harvard Medical School.*]

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SINCE the stomach gives no obvious external sign of its workings, investigators of gastric movements have hitherto been obliged to confine their studies to pathological subjects or to animals subjected to serious operative interference. Observations made under these necessarily abnormal conditions have yielded a literature[2] which is full of conflicting statements and uncertain results. The only sure conclusion to be drawn from this material is that when the stomach receives food, obscure peristaltic contractions are set going, which in some way churn the food to a liquid chyme and force it into the intestines. How imperfectly this describes the real workings of the stomach will appear from the following account of the actions of the organ studied by a new method. The mixing of a small quantity of subnitrate of bismuth with the food allows not only the contractions of the gastric wall, but also the movements of the gastric contents

[1] The first account of this work was given at the meeting of the American Physiological Society, in May, 1897 (see Science, June 11, 1897): and the later results were presented at the meeting of the Society in December, 1897. A summary of the results was published in the Proceedings of the American Physiological Society, this Journal, 1898, i, p. xiii. A report of the research was also made to the Boston Society of Medical Sciences, February 15, 1898.

[2] POENSGEN (Die motorische Verrichtungen des menschlichen Magens und ihre Störungen. Strassburg, 1882.) gives a comprehensive review of the literature to that date.

to be seen with the Röntgen rays in the uninjured animal during normal digestion. An unsuspected nicety of mechanical action and a surprising sensitiveness to nervous conditions have thereby been disclosed.

I. Introductory Literature.

The early writings on the subject of gastric movements are characterized by general inferences from physical laws and from the anatomical structure of the stomach. According to Galen,[1] the stomach had four functions: to draw the food from the mouth (*facultas attractrix*), to retain the food (*facultas retentrix*) during the process of chemical digestion (*facultas alteratrix*), and, finally, to pass the changed material onward (*facultas expultrix*). In later writings the *facultas attractrix* failed to appear as one of the functions of the stomach. Fallopius,[2] in the sixteenth century, changed the notion of the *facultas retentrix* by suggesting that the pylorus alone performed this office, and that the muscles of the gastric wall could help only by remaining quiet. Thus the *facultas alteratrix* and the *facultas expultrix* are left as true gastric functions. It is with the latter activity and its effects that this paper is concerned.

The ideas of the early writers concerning the pylorus and cardia are of interest. The cardia, they were agreed, is closed during normal digestion in order to keep the food from re-entering the œsophagus. The pylorus they looked upon as the ruler of the actions of the stomach. Such names as pylorus (keeper of the gate), janitor justus, and rector, which the first investigators gave to the sphincter, indicate their theories of its functions. The passage of chyme into the duodenum, the keeping of undigested food in the stomach, the act of vomiting, were all dependent, they believed, on the "will" of the pylorus.[3]

No substantial advance was made beyond these hypotheses until the beginning of the eighteenth century, when Wepfer and Schwartz applied the experimental method to the study of the gastric movements and laid the foundation of a more accurate knowledge. Wepfer[4] vivisected wolves, dogs, and cats, and observed constrictions following stimulation of the stomach. He remarked a general con-

[1] Galen: Opera omnia. Leipzig, 1822, iii, pp. 275, 281.

[2] Fallopius: Opera omnia; observationes anatomicæ. Frankfort, 1600, p. 412.

[3] Van Helmont: Opera omnia. Frankfort, 1707, p. 215.

[4] Wepfer: Historia cicutæ aquaticæ. Basel. 1679, p. 152 *et seq.*

traction of the pyloric part in vomiting (pp. 152, 168, and 250), and noted peristaltic and antiperistaltic movements passing over the organ. About the middle of the stomach he frequently saw a deep constriction. The investigations of Schwartz[1] are more valuable in that his search was for the normal action of the muscular coats. The movements, as he observed them, were generally only slight. They began either at the pylorus and passed to the left, half-way to the cardia, or started at the fundus and went to the pylorus. The contractions and relaxations, following one another, formed larger or smaller depressions and elevations, *i. e.*, more or less definite waves.

Near the middle of the last century, Haller,[2] after confirming the results obtained by Schwartz and Wepfer, summarized his knowledge of the motor functions of the stomach as follows: In general, contraction alternates with relaxation, so that the stomach is, now here, now there, made narrower by longitudinal or transverse depressions; then in these same places relaxation and bulging occur (pp. 260–262, and p. 276). So long as both apertures are closed the food is driven hither and thither by the shifting movements. It first takes a definite direction when the cardia or the pylorus opens. If the cardia opens, there is an antiperistalsis followed by regurgitation and vomiting (p. 281). If, on the contrary, the pylorus relaxes, a contraction, starting at the œsophagus, pushes the contents of the stomach into the duodenum. The pylorus allows the passage of fluids, but if it be stimulated by over distention or by hard pieces of food, it closes tightly (p. 277).

Such was the knowledge of gastric movements in Haller's time. A comparison of his descriptions with those in any standard work on physiology published ten or fifteen years ago will show that, despite very many researches, little advance had been made. Examinations of animals and men with gastric fistulas, studies of the stomach through the atrophied abdominal wall, and vivisection, have yielded numerous results, but these have not been harmonious, and have led to much controversy. Prominent in this mass of material as a valuable contribution are Beaumont's careful observations through the gastric fistula of Alexis St. Martin. Beaumont's work has recently been confirmed by Hofmeister and Schutz, who, with Rossbach, Hirsch, Openchowski, and others, have presented during the last twelve years

[1] B. Schwartz in Haller's Dissertationes anatomicæ. Göttingen, 1746, i, pp. 337–338.

[2] Haller: Elementa physiologiæ. Berne, 1764, vi, p. 260 *et seq.*

much new and interesting information. Since, however, it will conduce to clearness to set forth the results of these investigations in connection with my own work, their consideration will be deferred until later.

It will then appear that these later investigations, like the earlier researches, disagree as to the details of the stomach movements. Such differences in results are the proper outcome of the abnormal conditions under which the studies have been conducted. Obviously, in order to see the natural movements of the stomach, the organ should be observed in its natural state, and not after it has been disturbed by removal from the abdomen or by the adhesions and losses of substance incident to gastric fistulas.

As a means of watching the gastric motor activities under normal circumstances, Dr. H. P. Bowditch, in the autumn of 1896, suggested the use of the Röntgen rays. The present paper is the result of the work thus far completed. The kind assistance and stimulating counsel of Dr. Bowditch throughout the investigation are gratefully acknowledged.

II. The Method.

The method consists in mixing subnitrate of bismuth — a harmless, non-irritating powder — with the food, and observing the movements of the swallowed mass by means of the Röntgen rays. As is now generally known, the picture thrown on the fluorescent screen by the Röntgen rays is one of shadows of varying intensity; the denser the substance, the darker the shadow. There is nothing in the structure of the stomach to cause it to cast a different shade from that of its neighboring organs. But the dense bismuth powder, uniformly mixed with the food that fills the stomach, throws the dark shadow of the stomach contents on the screen, and the changes in the shape of the outlines indicate the intrinsic movements of the organ.

The animal used throughout the research was the cat. The meal given before making an observation consisted of from fifteen to eighteen grams of dry bread, softened to a mushy mass by milk, hot water, or thin gravy, and mixed with from one to five grams of subnitrate of bismuth, according to the purpose in hand. One or two grams of the bismuth compound produce a dim shadow of the stomach within which may be clearly seen the darker forms of food containing a larger amount of the substance; three grams are enough for ordinary observations; four or five grams are needed to

see the passage of food from the pylorus. The cat was usually kept from eating for at least twelve hours before an observation, in order that the stomach might be wholly free from contents transparent to the X-rays.

The construction of the holder on which the cat was tied is shown in the diagram (Fig. 1). It consisted of a framework supporting a sheet of black cotton cloth. The frame was made of two side pieces each 80 cm. long and 2.5 cm. square, connected at either end by blocks 2.5 cm. thick, 12.5 cm. wide, and 16 cm. long. The black cloth, which sagged for the comfort of the cat, was held by strips of wood nailed to the inner face of the frame. Through the side pieces were holes 0.6 cm. in diameter, and 5 cm. apart. Each of the leather nooses securing the legs went down through one of these holes, and up through another, in which it was made fast by forcing a pointed peg into the hole with it. The cat's head was held by two pegs, one on either side of the neck, joined above by a leather thong. One of the pegs was movable and could be put in any of the three holes, 3, 4.5, or 6 centimetres from the other peg, according to the thickness of the cat's neck.

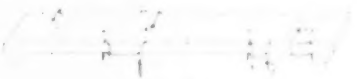

FIGURE 1.

For seeing the regular movements of the stomach the cat was tied back downward, with the fore paws in nooses at either side, and with the hind legs stretched out and fastened to the holder at the cat's right. For watching the passage of food from the pylorus, the hind legs were both fastened to the left side of the frame, so that the cat lay on her left flank. Most of the female cats would lie on the holder by the hour without making any attempt to break away or manifesting any signs of discomfort. In marked contrast was the behavior of the males. Almost without exception they seemed worried when fastened down. The interesting effects of these different ways of reacting to novel surroundings will be described later.

The cat-holder was supported at either end. Below it at a distance of 19 cm. was placed the tube generating the Rontgen rays. This tube had a self-regulating device for maintaining a uniform vacuum, — very useful in that it allowed long observations with rays of uniform intensity. A Topler-Holtz machine, run by a small motor, produced the electrical discharge through the tube. This apparatus

was placed behind the holder. The light from the tube and the machine was shut off from the observer by drapings of black cloth, so that in the dark room where the work was carried on it was possible to use an open fluorescent screen with sides only two centimetres high. This plan was found especially valuable in that it permitted tracing the outlines of the stomach on tissue paper laid over the fluorescent surface.

III. The Anatomy of the Stomach and its Relations to the Shadow.

It must be constantly borne in mind that the shadows described in this research are cast by the gastric contents, — not by the stomach itself. Therefore the movements of the organ are not seen directly, but are indicated by their effect on the contained food. Variations in the length and breadth of the stomach can be inferred from changes in the outline of the shadow, but variations in the front-to-back diameter of the organ must be judged from changes in the intensity of the shadow.

The form of the active stomach soon after food has been taken is shown in outline in Figure 2. Since the several parts of the stomach are to be mentioned frequently, it will be well to recall them here in their relations to the outline. The larger, cardiac part of the organ lies to the left of a line through *w x*. Into it the œsophagus opens through the cardiac sphincter, or cardia, at *c*. The pyloric part, which includes all of the stomach situated at the right of a line *w x*, is closed by the pylorus at *p*. This part has two divisions; the antrum at the right of the line *y z*, and the preantral part of the pyloric portion, or middle region of the stomach, between the lines *w x* and *y z*. The lesser curvature corresponds approximately to the anterior border of the shadow *c w p*; the greater curvature to the more extensive sweep, *c p*, along the posterior border.

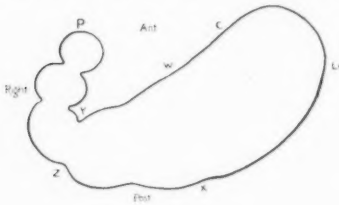

FIGURE 2.

The wall of the cat's stomach consists of three coats, but as this paper deals only with the functions of the muscular coat, that alone will be described. The gastric muscular fibres are disposed in three sets: an outer longitudinal layer, a middle circular layer, and a set

of inner oblique fibres. The longitudinal fibres continue those of the œsophagus, and, radiating over the cardiac end, become more marked along the curvatures than on the front and back surfaces. Over the antrum they lie in a thick, uniform layer. The circular fibres form a complete investment, and are arranged in rings at right angles to the curved axis of the stomach. Towards the pyloric end they become denser and stronger, and at the pylorus form a thick bundle, the pyloric sphincter. Separating the antrum from the rest of the stomach, at *y z*, is a special thickening of the circular fibres, called by the early writers[1] the "transverse band," and described by Hofmeister and Schütz[2] as the "sphincter antri pylorici." The oblique fibres start from the left of the cardiac orifice, and pass as two strong bands along the anterior part of the dorsal and ventral surfaces, giving off fine fasciculi to the circular musculature; towards the antrum they gradually disappear.

The musculature of the stomach consists of smooth muscle fibres, the chief physiological characteristics of which are slowness of contraction, rhythmic alternation of contraction and relaxation, and a very great tonicity, or power of prolonged contraction. The action of these muscles in the process of gastric digestion is now to be considered.

IV. The Normal Movements of the Stomach.

Since the time of Haller the chief contributors to the knowledge of the mechanics of the stomach have been Beaumont, Hofmeister and Schütz, and Rossbach.

Beaumont's famous investigations on Alexis St. Martin are recorded in almost all general works on physiology. Through a gastric fistula he introduced a thermometer-tube and observed how it was affected by the motions of the stomach. His conclusions are as follows: "The circular or transverse muscles contract progressively from left to right. When the impulse arrives at the *transverse band*, this is excited to a more forcible contraction, and, closing upon the alimentary matter and fluids contained in the pyloric end, prevents their regurgitation. The muscles of the pyloric end, now contracting upon the contents detained there, separate and expel some portion of the chyme. . . . After the contractile impulse is carried to the pyloric

[1] Beaumont: Physiology of digestion. Burlington, 1847, p. 104.

[2] Hofmeister and Schütz: Archiv fur exper. Pathol. und Pharmakol., 1886, xx, p. 7.

extremity, the circular band and all the transverse muscles become relaxed, and a contraction commences in a reversed direction, from right to left, and carries the contents again to the splenic extremity to undergo similar revolutions."[1]

In close accord with Beaumont's description of the activities of the human stomach are the records of the investigations on the stomach of dogs by Hofmeister and Schütz.[2] They removed the stomach from the body and placed it in a moist chamber, kept at body-heat and covered with glass. Under such conditions the organ remained active for from sixty to ninety minutes. A typical movement is described by these observers as composed of two phases. In the first phase a constriction of the circular fibres, deeper on the greater curvature, starts a few centimetres from the cardia and passes towards the pylorus. As the constriction proceeds it increases in strength until a maximum is reached about two centimetres in front of the antrum. This annular contraction, called by Hofmeister and Schütz the "preantral constriction," closes the first phase. Immediately thereafter the strong sphincter antri pylorici, or transverse band, contracts. Now, while the preantral constriction is relaxing, the sphincter antri pylorici tightens still more, and the antrum is shut off from the rest of the stomach. As soon as this has occurred a general contraction of the muscles of the antrum follows. Relaxation begins at the sphincter antri pylorici and progresses slowly toward the pylorus; it is sometimes accompanied by an antiperistaltic movement.

Although Rossbach[3] also used dogs his results vary considerably from those of Hofmeister and Schütz. This discrepancy is possibly accounted for by a difference in method, for Rossbach left the stomach in the body. The dogs were treated with morphia and curare, and the abdomen was then widely opened, so that the movements could be clearly seen. When the stomach was full Rossbach saw deep constrictions begin near the middle and pass in waves to the pylorus. At first these movements were weak: later, however, they became more vigorous. The fundus remained in tonic contraction about its contents and took no part in the peristalsis.

Before attempting to explain the difference in the records of these observers I shall give an account of what may be seen in a cat by use of bismuth subnitrate and the Röntgen rays.

[1] Beaumont: *loc. cit.*, p. 106.

[2] Hofmeister and Schütz: *loc. cit.*, p. 1.

[3] Rossbach: Deutsches Archiv für klinische Medicin, 1890, xlvi, p. 296.

1. **Movements of the Pyloric Part.** — Within five minutes after a cat has finished a meal of bread, there is visible near the duodenal end of the antrum a slight annular contraction which moves peristaltically to the pylorus: this is followed by several waves recurring at regular intervals. Two or three minutes after the first movement is seen, very slight constrictions appear near the middle of the stomach, and, pressing deeper into the greater curvature, course slowly towards the pyloric end. As new regions enter into constriction, the fibres just previously contracted become relaxed, so that there is a true moving wave, with a trough between two crests. When a wave swings round the bend in the pyloric part the indentation made by it deepens; and as digestion goes on the antrum elongates and the constrictions running over it grow stronger, but, until the stomach is nearly empty, they do not entirely divide the cavity. After the antrum has lengthened, a wave takes about thirty-six seconds to move from the middle of the stomach to the pylorus. At all periods of digestion the waves recur at intervals of almost exactly ten seconds. So regular is this rhythm that many times I have been able to determine within two or three seconds when a minute had elapsed simply by counting six similar phases of the undulations as they passed a given point. It results from this rhythm that when one wave is just beginning, several others are already running in order before it. Between the rings of constriction the stomach is bulged out, as shown in the various outlines in Figures 3, 4, and 5. The number of waves during a single period of digestion is larger than might possibly at first be supposed. In a cat that finished eating fifteen grams of bread at 10.52 A.M., the waves were running regularly at 11.00 o'clock. The stomach was not free from food until 6.12 P.M. During that time the cat was fastened to the holder at intervals of half an hour and the waves were always observed, following one another in slow and monotonous succession. At the rate of three hundred and sixty an hour, approximately two thousand six hundred waves passed over the antrum during that single digestive period.

From the above review, it will be manifest that my observations of the movements of the pyloric part agree closely with those of Rossbach, but differ considerably from the harmonious results of the work of Beaumont, and Hofmeister and Schütz. Beaumont's methods, however, may be justly criticised on the ground that the thermometer-tube which he held in the stomach was wholly unlike food and very liable to bring about unwonted contractions in so sensitive an organ

as the stomach. Further, the movements observed by Hofmeister and Schütz, as Ewald has pointed out,[1] may easily have resulted from the abnormal stimulus due to lack of blood — a potent cause of peristalsis. And it will be shown later that the accounts given by these investigators describe very well the actions of the stomach when stimulated by an unusual irritant. In this connection it may be added that since the publication of the preliminary notice of my work,[2] Roux and Bathazard,[3] using the Röntgen rays, have published the results of observations on the stomachs of the dog and man, similar to those thus far described in this paper.

The fact that my observations and those of Roux and Bathazard were conducted under normal conditions, and that the conditions of Rossbach's experiments were more nearly normal than those of the other observers mentioned, warrants the conclusion that the pyloric part has a more important function than that of merely expelling the contents of the stomach into the intestines. After summarizing the description given by Hofmeister and Schütz, Ewald, for *a priori* reasons, declares: "I cannot accept this view. The plain fact that the pyloric portion secretes a strongly digesting fluid containing pepsin and hydrochloric acid, proves it to be an important part for the peptonizing function of the stomach."[4] The account of the remarkable manner in which the pyloric portion performs this function must be deferred until the movements of other parts of the stomach have been considered.

2. **Movements of the Pyloric Sphincter.** — Rossbach[5] mars his otherwise careful work by declaring that the pylorus is tightly closed during the whole digestive period of from four to eight hours; and that then the sphincter relaxes and the peristaltic waves empty the stomach. That this is not the normal action of the sphincter has been shown by several observers. Hirsch[6] watched dogs with duodenal fistulas and saw food come from the stomach at intervals of one-fourth of a minute to several minutes. Roux and Bathazard[7]

[1] Ewald: Lectures on digestion. London, 1891, p. 66.

[2] Cannon: Science, June 11, 1897, p. 902.

[3] Roux et Bathazard: Comptes rendus de la soc. de biologie, 1897, 10 S. iv, pp. 704, 785, and Archives de physiologie, 1898, 5 S. x, p. 85.

[4] Ewald: *loc. cit.*, p. 67.

[5] Rossbach: Deutsches Archiv für klinische Medicin, 1890, xlvi, p. 317.

[6] Hirsch: Centralblatt für klin. Medicin, 1892, xiii, p. 994.

[7] Roux et Bathazard: Comptes rendus de la soc. de biologie, 1897, 10 S. iv, p. 705.

maintain that in dogs food enters the duodenum at the completion of each wave of constriction. Observations on the cat, however, do not support their view, but agree rather with the statement of Hirsch.

In cats fed with bread mixed with subnitrate of bismuth, ten or fifteen minutes elapse after the first constriction in the antrum before any food can be seen in the duodenum. When food does appear it is spurted through the pylorus and shoots along the intestine for two or three centimetres. Not every constriction-wave forces food from the antrum. On one occasion, about an hour after the movements began, three consecutive waves were seen, each of which squirted food into the duodenum. The pylorus remained closed against the next eight waves, opened for the ninth, but closed once more against the tenth and eleventh. For each of the four succeeding waves the sphincter relaxed, but blocked the food brought by three constrictions that followed; and in this irregular way the food continued passing from the stomach. Near the end of gastric digestion, when the constrictions are very deep, it may be that the pylorus opens for every wave.

When a hard bit of food reaches the pylorus, the sphincter closes tightly and remains closed longer than when the food is soft. This action of the sphincter was shown by giving with the regular food of the cat a dry, hard pellet of equal parts of starch paste and bismuth subnitrate, about the size of a pea. The food itself contained merely enough bismuth to throw a dim shadow, near the centre of which the pellet could be clearly seen as a dark object. The continual passing of the contraction-waves finally brought the little ball to the pylorus. When it arrived there, five grams of bismuth subnitrate were introduced into the stomach through a tube in the œsophagus. This was done in order that the food passing into the intestines after the ball came to the pylorus, might be distinguished from that which had gone on before. By kneading the stomach the bismuth was distributed, as shown by the uniformly black shadow. The pellet could still be seen near the end of the antrum when the constrictions passed over it. Now, although the waves continued to run regularly, the very black food did not gather in the intestines in sufficient amount to be recognized until forty-two minutes after it had been introduced. And when, finally, the food did show itself in the intestines, its shadow contrasted strongly with that of the food which had already passed on. The slowness of the expulsion is not to be regarded as wholly due to the

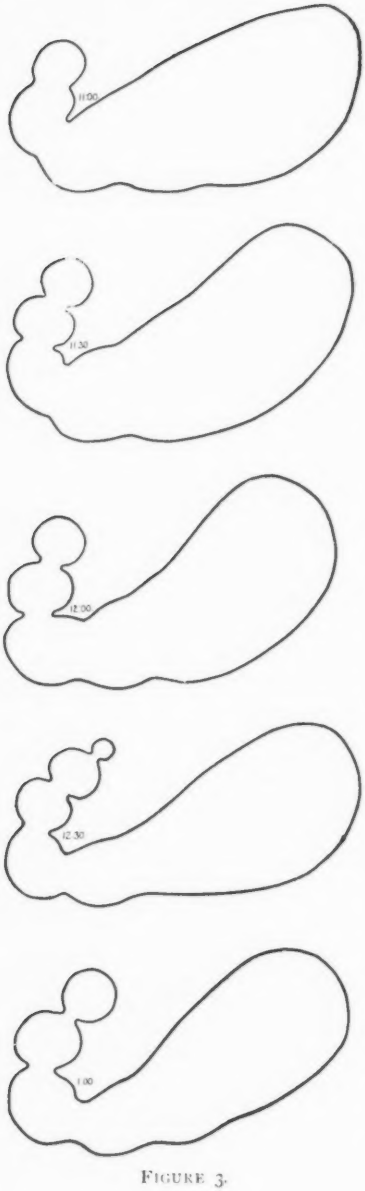

FIGURE 3.

hard mass. No doubt the kneading of the stomach mixed the contents of different parts of the organ and brought to the pylorus food not yet sufficiently digested to be passed by that selective sphincter. But this does not explain the whole delay. Food similar to that given here except that it contained no hard particles has usually been seen as small masses in the intestines within fifteen minutes after being swallowed. A part of the delay was evidently, therefore, caused by the hard pellet. Further evidence on this point was secured when, on one occasion, the sphincter was seen to open only seven times in twenty minutes following the arrival of a hard particle of food at the pylorus. The conclusion may therefore be drawn that hard morsels keep the pylorus closed and hinder the passage of the food into the duodenum.

3. **Activity of the Cardiac Portion.** —The part played by the fundus apparently has not hitherto been properly appreciated. It has been regarded as the place for peptic digestion or as a passive reservoir for food; but it is in fact a most interestingly active reservoir.

The action of the cardiac portion will be best understood by comparing the appearances the stomach presents at various stages in a digestive period. In order to show these stages I carefully made a set of three tracings of the out-

lines of the stomach as soon as possible after a cat had finished eating, and another set of three every half hour thereafter, until the contents had disappeared (Figs. 3, 4, and 5). These tracings were made by placing white tissue paper over the fluorescent screen, and drawing with a thick lead pencil, easily seen, as much of the boundary of the stomach as I could at the end of each expiration. Between the times for making the drawings the cat was allowed to rest quietly on a mat, but care was taken to lay her in the same position on the holder for every drawing. The drawings of each set were afterwards fastened over one another, so that the lines coincided as closely as possible. Another piece of tissue paper was then put over these, and all four sheets were laid on an illuminated pane of glass. It was thus easy to get a composite tracing, which, considering the movement imparted to the stomach by respiration, and the dimness of the shadows in the later stages of digestion, probably represents more exactly than any single drawing the outline of the stomach for each successive period.

A comparison of these drawings shows that as digestion proceeds the antrum appears gradually to elongate and acquire a greater capacity, and that the constrictions make deeper indentations in it. But when the fundus has lost most of its contents, the longitudinal and circular fibres of the antrum contract to make it again shorter and smaller. Its change of form, however, compared with the rest of the stomach, is slight.

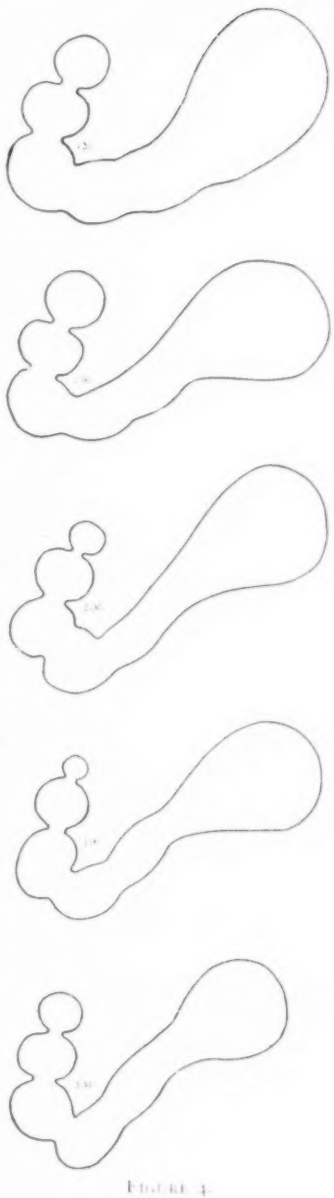

FIGURE 4.

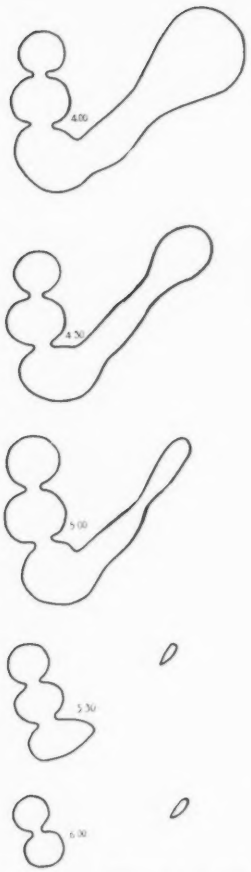

FIGURE 5. — Figures 3, 4, and 5 present outlines of the shadow of the contents of the stomach cast on a fluorescent screen by the Röntgen rays. The drawings were made by tracing the outline of the shadow on tissue paper laid upon the fluorescent surface, and are about one-half the actual size. They show the change in the appearance of the stomach at intervals of half an hour, from the time of eating until the stomach is nearly empty.

The first region to decrease markedly in size is the preantral part of the pyloric portion. The peristaltic undulations, caused by the circular fibres, start at the beginning of this portion, and gradually, by their rhythmic recurrence, press some of the contents into the antrum. As the process continues, the smooth muscle fibres with their remarkable tonicity contract closely about the food that remains, so that the middle region comes to have the shape of a tube (Fig. 4 — 1.30 P. M. to 2.30 P. M.), with the rounded fundus at one end and the active antrum at the other. Along the tube very shallow constrictions may be seen following one another to the pylorus.

At this juncture the longitudinal fibres which cover the fundus like radiating fingers, and the circular and oblique fibres reaching in all directions about this spherical region, begin to contract. Thus the contents of the fundus are squeezed into the tubular portion. This process, accompanied by a slight shortening of the tube, goes on until the shadow cast by the fundus is almost wholly obliterated (Fig. 5 — 5.30 P.M.).

The waves of constriction moving along the tubular portion press the food onward as fast as they receive it from the contracting fundus; and when the fundus is at last emptied they sweep the contents of the tube into the antrum (Fig. 5 — 5.00 P.M. to 6.00 P.M.). Here the operation is continued by the deeper constrictions till finally (in this instance, at 6.12 P. M.) with the exception of a slight trace of food in the fundus, nothing is to be seen in the stomach at all.

The food in the fundus may possibly be

slightly affected by the to-and-fro movements of the diaphragm in respiration. With normal breathing the upper border of the cardiac portion swings through about one centimetre; with dyspnœa, or deep breathing, through one and a half or two centimetres. Since the lower border does not move so much, the contents are gently pressed, and then released from pressure, at each respiration. The pyloric portion is moved very little by the diaphragm, the oscillation being less than a half centimetre.

Moritz[1] has pointed out the value of an organ like the stomach for holding the bulk of the food and serving it out a little at a time so that the intestines may not become congested during their digestive and absorptive processes. All of the advantages supposed to be thus secured to the intestines may be claimed also for the stomach itself. For the preceding description indicates, and experiments to be described later prove, that the stomach is composed of two physiologically distinct portions: the busy antrum, over which during digestion constriction-waves are running in continuous rhythm; and the cardiac part, which is an active reservoir, pressing out its contents a little at a time as the antral mechanism is ready to receive them.[2]

V. The Movements of the Stomach in Vomiting.

The appearance of the stomach during vomiting has been studied particularly by Openchowski.[3] He says that when an emetic is given there follows a quivering of the stomach wall, which, beginning near the pylorus, shows itself later in the antral and middle regions of the stomach. The quivering afterwards passes into a contraction, most strongly marked in the antral part, since the peristaltic waves running down to the antrum from above are continually growing deeper. At the same time the fundus expands spherically. The increased contraction in the pyloric part drives the contents towards the more dilated portion, and thence they are forced into the œsophagus by abdominal pressure.

The same phenomena occur when a cat is given apomorphine hypo-

[1] Moritz: Münchener med. Wochenschrift, 1895, xlii, p. 1146.

[2] By study of the pressure at various parts of the stomach in man, Moritz (Zeitschr. f. Biologie, 1895, xxxii, p. 350), and von Pfungen (Cbl. f. Physiol., 1887, i, p. 220), have inferred that the fundus must be quiet and that the motor functions are performed by the pyloric part. Leven has also expressed the same conclusion: Traité des maladies de l'estomac, Paris, 1879, p. 16.

[3] Openchowski: Archiv für Physiologie, 1889, p. 552.

dermatically. First the upper circular muscles relax and become so flaccid that the slightest movement of the abdomen changes the form of the fundus. Then there are apparently irregular twitchings of the fundus wall. Soon a deep constriction starts about three centimetres below the cardia, and, growing in strength, moves toward the pylorus. When it reaches the transverse band the constriction tightens and holds fast, while a wave of contraction sweeps over the antrum. Another similar constriction follows. In the interval the transverse band relaxes slightly, but tightens again when the second wave reaches it. Perhaps a dozen such waves pass; then a firm contraction at the beginning of the antrum completely divides the gastric cavity into two parts. This same division of the stomach into two parts at the transverse band is to be seen when mustard is given. Now, although the waves are still running over the antrum, the whole preantral part of the stomach is fully relaxed. A flattening of the diaphragm, and a quick jerk of the abdominal muscles, accompanied by the opening of the cardia, now force the contents of the fundus into the œsophagus. As the spasmodic contractions of the abdominal muscles are repeated, the gastric wall again tightens around the contained food. Antiperistalsis I have seen only once; then, while the cat was retching, a constriction started at the pylorus and ran back, over the antrum, completely obliterating the antral cavity.

It will be recalled that the principal difference between the movements of the stomach and their effects as described by Beaumont, and Hofmeister and Schütz on the one hand, and Rossbach, Roux and Bathazard, and myself on the other hand, is that the former observed constrictions completely dividing the stomach at the transverse band, and the antrum then squeezing its contents into the intestines; whereas the latter have seen the constrictions moving forward as narrowing rings, but not separating the gastric cavity into two parts.

With the exception of peristalsis in the antrum, the gastric movements at the beginning of emesis are almost exactly the same as those Beaumont, and Hofmeister and Schütz, declare to be the normal contractions of the stomach. Their observations were made, however, when the organ was subjected to unnatural stimulation. In the excised stomach, observed by Hofmeister and Schütz, not only were all nervous connections severed, but likewise all flow of blood to the organ was entirely stopped, and the cutting off of the blood supply is regarded as one of the most powerful predisposing causes of peristal-

tic action.[1] The thermometer-tube used by Beaumont was an irritant to the stomach, as he himself admits. "If the bulb of the thermometer," he writes,[2] "be suffered to be drawn down to the pyloric extremity, and retained there for a short time, or if the experiments be repeated too frequently, it causes severe distress, and a sensation like cramp, or spasm, which ceases on withdrawing the tube, but leaves a sense of soreness and tenderness at the pit of the stomach." Moritz also noticed that a rubber sound introduced into the human stomach proved to be a source of irritation.[3] It seems reasonable to suppose, therefore, that these observers did not see the normal movements, but the actions resulting from abnormal irritation.

VI. The Effect of the Movements of the Stomach on the Food.

In my first observations on the active stomach a bulging of the stomach-wall was to be seen in front of the passing waves. But as food did not immediately appear in the intestine, and as, after the pylorus relaxed, the gastric contents did not diminish rapidly enough to allow the supposition that all of the food squeezed forward by the waves was immediately forced through the pylorus, it was assumed that a part, at least, of the food under pressure was forced back towards the cardia through the constriction-ring. This inference was stated in the preliminary notice of my work.[4] Roux and Bathazard also observed the passage of the undulations over the pyloric part, but state merely that the function of the constrictions is the propulsion of food into the intestine, without mentioning what must be regarded as a very important function, namely, the mixing effect of the waves.

Most writers have agreed that the result of the active and passive movements of the stomach is to force the contents hither and thither, thus mixing them and the gastric juice together. Two observers, Beaumont and Brinton, have attempted to explain the manner of the mixing. Beaumont, after noting how the thermometer-tube, used by him to indicate the gastric motions, was affected, describes the circulation of the food as follows: "The bolus as it enters the cardia turns

[1] Mall: A study of the intestinal contraction. Johns Hopkins hospital reports, i, p. 70.

[2] Beaumont: *loc. cit.*, p. 105.

[3] Moritz: Zeitschr. f. Biologie, 1895, xxxii, p. 369.

[4] Cannon: Science, June 11, 1897, p. 902.

to the left; passes the aperture; descends into the splenic extremity; and follows the great curvature towards the pyloric end. It then returns, in the course of the small curvature, makes its appearance again at the aperture, in its descent into the great curvature, to perform similar revolutions."[1] Brinton[2] bases his theory of the circulation of the food on an analogy between the movement of a constriction over the stomach, and the passage of a septum with a central perforation along the interior of a cylinder full of liquid. The result in both cases, he declares, must be a peripheral current of advance, and a central current of return. Thus in the stomach there would be peripheral currents from the cardia along the walls of the stomach to the pylorus, where they would unite and run as an axial current back to the cardia.

Certain *a priori* objections may be urged against each of these conclusions. In the first place, Beaumont's observations were made on a subject having a gastric fistula, and the adhesions between the stomach and the abdominal wall would prevent the fundus from acting quite normally in relation to its contents. Beaumont's conclusions, furthermore, are based on the movements of a thermometer-tube introduced through the fistula, and on the recognition of particles of food which he had seen before as they passed the fistulous opening: the first method, as has been shown, made the conditions in the stomach more abnormal than they were previously; the second gave uncertain knowledge of the course of the food when out of the observer's sight. Brinton's hypothesis states the probable movements of fluid contents acted on by a passing constriction. But it may be objected that the conditions assumed by him do not exist in all parts of the stomach. For, not only is there no peristalsis visible in the fundus, but with the usual food the fundus contents are not liquid. Moreover, the constrictions at the beginning of the pyloric portion are very slight, and move slowly. The food in front of them is, accordingly, not under much greater pressure than the food behind them. The axial current which might result, therefore, could not be strong enough to go far into the cardiac portion.

It is easily possible to test experimentally the validity of these two theories by watching the action of pieces of food which throw a black shadow in a dimly-outlined stomach. For this purpose little paste pellets of bismuth subnitrate, with starch enough to keep the

[1] BEAUMONT: *loc. cit.*, p. 101.

[2] BRINTON: The diseases of the stomach. Philadelphia, 1865, p. 24.

form, were given with the customary meal. These pellets, it was found, did not break up in the stomach during the gastric digestion of soft bread. Several times I have been fortunate in getting two of the little balls in the axis of the stomach and about a centimetre apart. As the constriction-wave approached them, both moved forward, but not so rapidly as the wave. Now when the constriction overtook the first ball, the ball moved backward through the constricted ring, in the direction of least resistance. The wave then overtook the second ball, and it also passed backward to join its fellow. At the approach of the next wave they were both pushed forward once more, only to be again forced backward, one at a time, through the narrow orifice. As the waves recurred in their persistent rhythm, the balls were seen to be making progress — an oscillating progress — towards the pylorus; for they went forward each time a little farther than they retreated. This to-and-fro movement of the pellets was much more marked in the antrum, where the waves were deep, than in the middle region. On different occasions from nine to twelve minutes have elapsed while the balls were passing from where the waves first affected them to the pylorus; which means that on the way they were moved back and forth by more than a half hundred constrictions.

If the pylorus does not relax, it is evident that a wave approaching it pushes the food into a blind elastic pouch, the only exit from which is through the advancing constricted ring. The constrictions are deeper near the end of the antrum, and the rings are small; consequently the food is squirted back through them with considerable violence. As has been noted, the pylorus opens less frequently for a while after a solid piece of food comes to it. In such a case the slow driving waves squeeze the hard morsel and the soft food about it up to the sphincter, only to have the whole mass shoot back, sometimes half way along the antrum. Over and over again the process is repeated till the sphincter at last opens and allows the more fluid parts to pass. Hofmeister and Schutz, and Moritz have disclaimed any selective action of the pylorus, and declare that solids are driven from the pylorus to the fundus by antiperistalsis. The action of the pylorus which I have seen, however, is more like that described by the earlier investigators; for during digestion there was no antiperistalsis, and the sphincter, separating the fluids from the solids, caused the solids to remain and undergo a tireless rubbing. Frequently when several of these balls have been given at the same time, they

have all been seen in the antrum after the stomach was otherwise empty. Here they remain to be softened in time by the juices or to be forced through the pylorus later, for solids do pass into the intestine. Thus when the teeth neglect their work the stomach attempts to perform their function; the relative inefficiency of the gastric method of grinding and its interference with the normal gastric activities point an obvious hygienic moral.

During the process of digestion the food in the cardiac portion gives no sign of currents. Balls which lie in the fundus immediately after the food is ingested, keep their relative positions until the cardiac portion begins to contract, and then move very slowly towards the antrum. Moreover, the food in the fundus of a cat has the same mushy appearance when examined after gastric peristalsis had been active for an hour and a half that it had when ingested. The contents of the antrum, on the other hand, look quite different and have the consistency of thick soup. The inactivity of the food in the fundus can also be proved by feeding first five grams of bread and bismuth, then five grams without bismuth, and finally five grams again with bismuth in it. The stomach contents are thus arranged in two dark layers along the curvatures, with a light layer between. Tracings made on tissue paper show that ten minutes after peristalsis commenced, the stratification had entirely disappeared in the pyloric part, but that an hour and twenty minutes thereafter the layers were still clearly visible in the cardiac region.

The value of the circulation of the food, as described by Beaumont and Brinton, lay in the supposition that the contents of the stomach were thus brought near to the secreting gastric wall, and that the gastric juice could thus more readily exert its action. Although my observations do not support their theories of mixing currents running throughout the stomach, they still show that the pyloric portion is an admirable device for bringing all of the food under the influence of the glandular secretions of that region. For, when a constriction occurs, the secreting surface enclosed by the ring is brought close around the food lying within the ring in the axis of the stomach. As this constriction passes on, fresh areas of glandular tissue are continuously pressed in around the narrow orifice. And also, as the constriction passes on, a thin stream of gastric contents is continuously forced back through the orifice and thus past the mouths of the glands. The result of this ingenious mechanism is that every part of the secreting surface of the pyloric portion is brought near to every bit

of food, before the latter leaves the stomach, a half hundred times or more, as evidenced by the moving ball.

VII. Salivary Digestion in the Stomach.

The absence of movement in the fundus would seem to give the food during its stay there little opportunity to become mixed with the gastric juices and thus to undergo peptic digestion. The truth of this supposition can easily be proved experimentally by feeding a slightly alkaline meal and later testing the chemical reaction of the contents of various parts of the stomach. A cat which had been without food for fifteen hours was given eighteen grams of mushy bread made slightly alkaline with sodium carbonate. One hour and a half after the cat had finished eating, she was killed and the stomach laid bare by opening the abdomen. A very small hole was then made through the wall in the fundus region, and another similar hole was made into the antrum. By means of a glass pipette food was extracted first from the periphery of the fundus; this food was slightly acid. The cleaned pipette was then introduced two and a half centimetres into the fundus contents and the food thus extracted gave the original alkaline reaction. Specimens of the liquid contents of the antral and middle regions, taken from various depths, were all strongly acid. A dog killed an hour and three-quarters after eating showed similar differences between the reactions of the food in the fundus and the food in the pyloric portion. So, as a matter of fact, the food does not become acid at a uniform rate in all parts of the stomach, as would be the case if Beaumont's and Brinton's theories of mixing currents were true. Moreover, if the facts accorded with their notions, the saliva, which ceases to act in the presence of more than 0.003 per cent free hydrochloric acid,[1] and is destroyed when the percentage of acid proteids is large, would manifestly have its service as a ferment limited to the relatively short time during which the stomach contents, in the process of thorough mixing, were reaching that degree of acidity. There is, however, no movement of food in the fundus, and the alkaline food received from the œsophagus remains alkaline in this region for a considerable period. The nutriment, therefore, if well chewed and thus mixed with saliva, can undergo salivary digestion in the fundus for a considerable period without interference by the acid gastric juice.

[1] Chittenden and Smith: Chemical news, London, 1886, liii, p. 173.

From all these observations the conclusion must be that the fundus acts as a reservoir for the food, in which the digestion of sugars and starches may take place; and that the pyloric portion with its simple but marvellous peristaltic mechanism, by a single process, triturates the food, brings it near to the active glands, stirs it thoroughly with their secretions, and expels the products into the intestines.

VIII. The Inhibition of Stomach Movements during Emotion.

Early in the research a marked unlikeness was noticed in the action of the stomachs of male and female cats. The peristalsis seen with only a few exceptions in female cats failed to appear in most of the males, although both had received exactly the same treatment. Along with this difference was a very striking difference in behavior when bound to the holder; the females would lie quiet, mewing occasionally, but purring as soon as they were gently stroked. The males, on the contrary, would fly into a violent rage, struggle to be loose from their fastenings, bite at everything near their heads, cry loudly, and resist all attempts to quiet them. On account of this difference only female cats were used for some time; and the significance at first attributed to the action of the males, was almost forgotten when the following incident recalled it, and suggested that the excitement caused the suspension of the stomach movements. On October 23, 1897, a male cat was fed at 12.00, but was not placed on the holder till ninety minutes later. The waves were passing at the rate of six a minute. The cat fell into a rage and the waves suddenly stopped.

A few days later an observation on a female with kittens explained the absence of gastric movements in the males. While the peristaltic undulations were coursing regularly over the cat's stomach, she suddenly changed from her peaceful sleepiness, began to breathe quickly and struggled to get loose. As soon as the change took place, the movements in the stomach entirely disappeared; the pyloric portion relaxed and presented a smooth rounded outline. I continued observing, and stroked the cat reassuringly. In a moment she became quiet and began to purr. As soon as this happened the movements commenced again in the stomach; first a few constrictions were visible near the end of the antrum, then a few near the sharp bend in the lesser curvature, and finally the waves were running normally from their habitual starting place. By holding the cat's mouth closed between the thumb and last three fingers and covering her nostrils with

the index finger, she could be kept from breathing. At the first sign of discomfort the fingers were removed. This experiment was repeated a great many times on different cats, and invariably the evidence of distress was accompanied by a total suspension of the motor activities of the stomach and a relaxation of the antral fibres.

No amount of kneading or compression of the abdomen with the fingers, short of making the cat angry, would cause the waves to stop; so that the cat's movements, in themselves, were not the source of the inhibition. And since expressions of strong feeling on the part of the animal always accompanied cessation of the constriction-waves, the inhibition was probably due to nervous influence. It has long been common knowledge that violent emotions interfere with the digestive process, but that the gastric motor activities should manifest such extreme sensitiveness to nervous conditions is surprising.

Summary.

1. By mixing a harmless powder, subnitrate of bismuth, with the food, the movements of the stomach can be seen by means of the Röntgen rays.

2. The stomach consists of two physiologically distinct parts: the pyloric part and the fundus; over the pyloric part, while food is present, constriction-waves are seen continually coursing towards the pylorus; the fundus is an active reservoir for the food, and squeezes out its contents gradually into the pyloric part.

3. The stomach is emptied by the formation, between the fundus and the antrum, of a tube along which constrictions pass. The contents of the fundus are pressed into the tube and the tube and antrum slowly cleared of food by the waves of constriction.

4. The food in the pyloric portion is first pushed forward by the running wave, and then by pressure of the stomach wall is returned through the ring of constriction; thus the food is thoroughly mixed with gastric juice, and is forced by an oscillating progress to the pylorus.

5. The food in the fundus is not moved by peristalsis and consequently it is not mixed with the gastric juice; salivary digestion can therefore be carried on in this region for a considerable period without being stopped by the acid gastric juice.

6. The pylorus does not open at the approach of every wave, but only at irregular intervals. The arrival of a hard morsel causes the

sphincter to open less frequently than normally, thus materially interfering with the passage of the already liquefied food.

7. Solid food remains in the antrum to be rubbed by the constrictions until triturated, or to be softened by the gastric juice, or later it may be forced into the intestine in the solid state.

8. The constriction-waves have, therefore, three functions: the mixing, trituration, and expulsion of the food.

9. At the beginning of vomiting the gastric cavity is separated into two parts by a constriction at the entrance to the antrum; the cardiac portion is relaxed and the spasmodic contractions of the abdominal muscles force the food through the opened cardia into the œsophagus.

10. The stomach movements are inhibited whenever the cat shows signs of anxiety, rage, or distress.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE CARDIAC NERVES IN THE GUINEA-PIG.

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WHILE the guinea-pig has been used largely in experimental pathology, it seems to have been used little as yet in physiological research; in the literature to which I have had access I have noticed but two references to the physiology of the heart or of the cardiac nerves of this animal. In papers published by Legros and Onimus[1] and by MacWilliam[2] references are made to the effect upon the heart of stimulating the vagus nerve in the guinea-pig; it is evident, however, that their experiments upon this animal were very limited in number. The fact that the guinea-pig is used so extensively in experimental pathology may give some interest to the experiments described in this paper.

I. Method of Experimenting.

The guinea-pigs used in these experiments were of various sizes; the average weight, however, was 584 grams. Animals of both sexes and of various ages were used.

Anæsthetics. The animals were thoroughly anæsthetized in all cases. The anæsthetics used in the various experiments were ether, given by inhalation; chloral hydrate, opium, and morphine, these three given subcutaneously, either singly or in various combinations. When chloral was used alone, 0.5 gram was given a short time before beginning the operation. Smaller doses were given as required during the experiment. Of opium and chloral I have used 1 cubic centimetre of the deodorized tincture of opium combined with 0.25 gram of chloral; of morphine and chloral I have used 0.005 gram of morphine combined with 0.25 gram of chloral. It is usually advisable to give a little ether by inhalation while the dissection is performed.

[1] Legros et Onimus: Journal de l'anatomie et de la physiologie, 1872, pp. 575 and 578.

[2] MacWilliam: Journal of physiology, 1888, ix, p. 387.

Recording of blood-pressure. The blood-pressure was measured by means of a cannula inserted into the proximal stump of one of the carotid arteries. As the arteries of the guinea-pig are very small and the tissues very delicate, the insertion of a cannula into one of the carotids frequently offers difficulties. The following method was found to be of great assistance in performing this operation. After the artery had been dissected from the sheath it was clamped and divided and a fine silk thread was tied to the proximal stump just above the point at which the opening in the artery for the cannula was to be made. The artery was then lifted from the wound and slightly stretched, and the thread attached to the artery was held in the operator's teeth, — a procedure which left one hand free for the use of the forceps and the other to hold the cannula. Moreover, taking the thread in the teeth seems to inhibit the ordinary reflexes of the operator's body and thus he is better enabled to work with a steady hand. The blood-pressure was recorded by a mercurial manometer on the smoked paper of a drum-kymograph, the fineness of the tracing usually obtained being too great for the use of ink to be satisfactory. For excitation of the nerves the faradic current of an ordinary du Bois-Reymond induction coil was used; the current for the primary coil was obtained from an electric-light dynamo, and was maintained at a little less than one ampère, by throwing in the necessary amount of resistance. The interruption of the primary current was by Neef's electro-magnetic hammer. Small shielded electrodes of platinum were used.

Normal blood-pressure. The average mean blood-pressure (corrected for the weight of the solution of sodium carbonate) as determined upon guinea-pigs anæsthetized by one or more of the above-mentioned drugs, was 75 millimetres of mercury; the highest blood-pressure observed was 111 mm., the lowest, 56 mm. The average rate of the heart-beat was 200 per minute, the fastest and slowest rates observed being 288 and 132 respectively. The average number of respirations per minute of animals quiet in their cage (the temperature of the room being 20° C.) was 72 per minute.

II. The Vagus Nerve.

The vagi were investigated after exposure in the neck, where they occupy about the same anatomical position in the guinea-pig as in other mammals.

Section of the vagi. Section of both vagi in the guinea-pig seems to have little effect upon either the rate of the heart or the blood-pressure. In a few cases slight acceleration was noticed for a short time after the section; but this usually gave place, within ten or twenty seconds, to the normal rate. Much more frequently section was followed by a slight slowing of the rate of the heart during the first ten seconds, this probably being caused by mechanical stimulation of the inhibitory fibres. In no case was a rise of blood-pressure observed to follow section of both vagi. Thus the inhibitory nerves of the heart of the guinea-pig do not seem to be in constant activity.

Stimulation of the vagus; effect of the season upon the result. Meyer has shown that the effect upon the heart of stimulation of the vagus nerve is much more marked in the cold-blooded animals than in the warm-blooded ones, and other investigators have confirmed Meyer's conclusions.[1] Since vagus inhibition is less effective in the case of the more frequently beating hearts of warm-blooded animals, the question naturally suggests itself whether in such hearts as that of the guinea-pig, of which the average number of pulsations per minute is 200, the inhibitory power of the vagi is sufficient to bring the heart to a standstill.

My work on the guinea-pig was begun in October, 1896. It was suspended during November and December and resumed in January, 1897. It was continued through January, February, March, and April. For convenience the time may be divided into two periods, an early period, from October until the end of January, and a later period, including the latter part of February, March, and April. During each of these two periods the results of vagus stimulation differed quite markedly from the results obtained during the other period, the curve of inhibition being characteristic of the period in which it was taken. During the first period, *i. e.*, from October to January, cardiac inhibition from excitation of the vagi was much less marked than during the second period from February to April. In no case during the first period was I able to bring the heart to a standstill, no matter how strong a current was applied to the vagus, and I came to the conclusion that in at least one of the warm-blooded animals with a very frequently beating heart, *i. e.*, the guinea-pig, the inhibitory power of the vagus was not sufficient to bring the heart to a standstill. During the first weeks in February, however, I was surprised to find that in one guinea-pig the heart was stopped by a faradic current

[1] See HOUGH: Journal of physiology, 1895, xviii. p. 161.

of only moderate strength. For a short time after this I noticed that in some guinea-pigs the heart was stopped by a moderately strong current (the secondary coil being at about 10 cm.), whereas in others the strongest current used (the secondary coil being at 0 cm.) was unable to stop it. During the latter part of February and throughout March and April the heart was invariably brought to a standstill by faradic currents of the strength commonly used in physiological work, *i. e.*, just perceptible when applied to the tongue. In some cases very weak currents, such as are obtained when the secondary coil stands at 24, 28, and 30 centimetres from the primary, sufficed to cause stoppage.

The curves of inhibition obtained during the first period differed in several respects from those obtained during the second period. In the former (see Fig. 1) the slowing of the heart and the fall of blood-

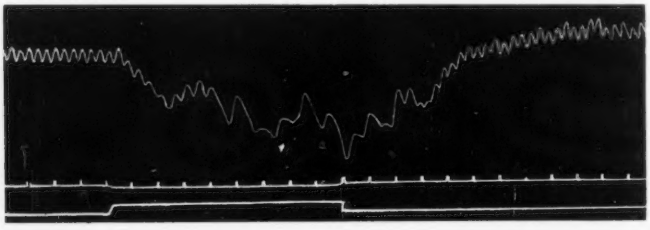

FIGURE 1. Inhibition from stimulation of the left vagus, with the secondary coil at 5 cm. Time in seconds. The line of zero pressure is not shown. The writing-points of the manometer and of the stimulating key were in the same vertical line.

pressure were gradual; the fall of pressure was not very great in proportion to the normal blood-pressure, which as a rule was considerably higher during the first than during the second period. The return of the blood-pressure and the heart-rate to the normal, after the cessation of stimulation, was gradual and fairly regular, and inhibition was followed by comparatively little irregularity of heart-rate or of blood-pressure. On the other hand, during the second period the stopping of the heart and the fall of blood-pressure were sudden, the descent in the curve being sometimes almost vertical (see Fig. 2). The blood-pressure was very irregular after the cessation of stimulation, sometimes failing to return to the ordinary height, while more frequently it rose far above it and then gradually returned to it or fell below it.

At about the season when it was first noticed that excitation of the vagus was bringing the heart to a standstill, it was also noticed that the guinea-pigs under experiment did not live as long as they had formerly done. Later it was noticed that they died very easily, and without any apparent cause; no sooner were the necessary dissections made, and the artery connected with the manometer, than the animal died. Although the anæsthetics were used with great care, and various ones were tried, there was no improvement. At the season in question the dissection was done more carefully and more rapidly than during October, and everything pertaining to the operation was more favorable than during the earlier months; still the animals died before any results of value could be obtained. In many cases the tissues of the neck showed an unduly venous condition of the blood before the cannula was inserted into the artery; respiration ceased; the heart

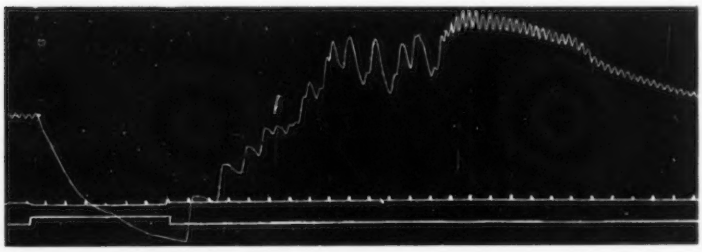

FIGURE 2. Four-fifths the original size. Inhibition from stimulation of the left vagus with the secondary coil at 16 cm. Time in seconds. The line of zero pressure is not shown. The writing-points of the manometer and of the stimulating key were in the same vertical line.

became feeble, and the animal died. The heart usually continued to beat for a short time after respiration had ceased; artificial respiration, however, did not prolong the life of the animal. In April it became practically impossible to get any results whatever from the experiments. In order to be certain that the trouble was not wholly with the special lot of animals on hand, or with the hygienic conditions to which they were exposed, a new lot of animals was procured, but the results were not improved except in a few cases. The only possible explanation of these results seems to be that the lack of vitality was due either to some unknown cause associated with the season of the year, or to the diminution of fresh air and light during the winter months, or to both causes combined. Nearly every one has

experienced in his own person a certain diminution of vitality during the spring months. It is a well-known fact that persons suffering from chronic diseases are much more liable to die during March and April than during other months of the year; and eminent surgeons state that major operations are more liable to be followed by death during those months than at other seasons. There would seem, however, to be some slight evidence in favor of the view that diminution of fresh air and light during the winter months is partially responsible for this lack of vitality in the guinea-pigs, from the fact that, of the last lot of the guinea-pigs used, a few, which had been placed in the sunlight in a specially well ventilated room for two weeks, showed greater vitality than those of the same lot kept elsewhere, although much less vitality than those subjected to experiment from October to January. Hygienic influences alone, however, do not suffice to explain the differences of vitality observed.

It seems clear from what has been said that, in the guinea-pig at least, the efficiency of the stimulation of the inhibitory nerves of the heart is inversely proportional to the degree of vitality possessed by the animal. In a measure this agrees with the opinion expressed by Hough,[1] who states that in his experiments upon cats, when the heart from any cause has been weakened and the pulse has become feeble, stimulation of the vagi has been much more effective than when the heart was vigorous; the slowing of the heart and the fall of blood-pressure being much more pronounced. I did not find, however, that in the guinea-pig when the heart had been weakened from profound anæsthesia, from shock, or from loss of blood, stimulation of the vagi was more efficient, for in no case during the earlier period, from October to January, no matter what was the condition of the animal, did stimulation of the vagi stop the heart. Hough states that in the cat the heart can rarely be brought to a complete standstill, not oftener, I think, than once in twenty cases. I do not know at what season of the year his experiments were made, or in what conditions the animals upon which he operated were kept, but in two of three experiments upon cats which I made in April the heart was brought to a standstill and maintained at a standstill for periods of half a minute when the vagus was stimulated with a faradic current of moderate strength.

After-effects of stimulation of one vagus. After the cessation of a stimulation of the vagus during which the heart had been slowed or

[1] Hough; *op. cit.*, p. 164.

brought to a standstill, the beat usually returned quickly to its previous rate, and there was neither a secondary acceleration, as is often observed when the vagus of the dog has been stimulated, nor a long-continued slowing, such as occurs frequently when the vagus of the opossum [1] has been stimulated. The blood-pressure after stimulation of the vagus was, however, often very irregular; this irregularity was much more marked in the spring than in the autumn or winter months. These irregularities of the blood-pressure were frequently accompanied by irregularities of the heart-rate.

During the months of the spring, however, there sometimes occurred even before stimulation, and without any apparent cause, marked irregularities of the blood-pressure and the heart-rate, whereas during the autumn months one of the most striking characteristics of the tracing had been the great regularity of the blood-pressure and of the heart-rate; as a rule, the latter varied very little in the course of a long experiment, but continued almost the same till the animal was at the point of death. In fact, during the spring months there seemed to be a want of stability or of general tone on the part of the heart and perhaps of the vaso-motor system, a condition which seems to me to resemble that which I have observed in frogs in the spring, when studying the form of the muscle-curve with the pendulum-myograph: the muscle-curves being very irregular although the conditions of the experiments were kept as nearly constant as possible.

Rise of blood-pressure following stimulation of the vagus. At times, after the cessation of a stimulation of the vagus in the guinea-pig, the blood-pressure rose far above its original height (see Figs. 2 and 3); in one case it was doubled. The cause of such a marked rise of blood-pressure following inhibition deserves investigation. One explanation of this phenomenon which might be suggested is that the vagus nerve is the trophic nerve of the heart, that stimulation of this nerve causes constructive metabolism to be induced during the period of inhibition, and that the heart is thus "nursed into more vigorous activity." The "good effects" upon the heart of vagus inhibition artificially induced in the warm-blooded animals may, I think, be questioned. My experience with the guinea-pig would seem to support the view that caution should be used in drawing very detailed conclusions with regard to specific physiological conditions in one kind of animals from experimental work on animals very

[1] HUNT and HARRINGTON: Journal of experimental medicine, 1897, ii, p. 715.

different morphologically and, in general, physiologically. The infrequently beating hearts of the cold-blooded frog and turtle are very different in several respects from the frequently beating hearts of the warm-blooded rabbit and guinea-pig. The opinion that inhibition caused by vagus stimulation is beneficial to the heart is largely the

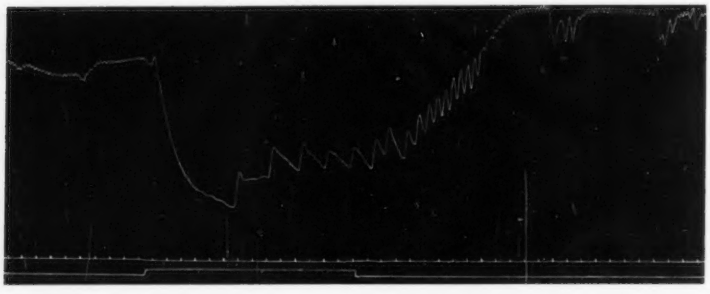

FIGURE 3. Three-fifths the original size. Inhibition from stimulation of the right vagus of the guinea-pig with the secondary coil at 15 cm. Time in seconds. The line of zero pressure is not shown. The writing-points of the manometer and of the stimulating key were in the same vertical line.

result of the teaching of Gaskell, but it must be remembered that Gaskell concludes his paper [1] by stating that his observations were confined to the cold-blooded animals, and that he is "not yet in position to say how far, in the more highly-developed mammalia, the phenomena of the heart may have become changed under a greater differentiation of function, and an increased complexity of structure." Immediate supply of nutriment is a matter of comparatively little importance to the cold-blooded hearts; it is a matter of the greatest importance to the very frequently beating warm-blooded hearts. "The two organs of the body whose supply of oxygenated blood cannot be interrupted, even temporarily, without danger to the system are the central nervous system and the heart." [2] "The force of the ventricular contraction is immediately affected by a change in the amount of blood supplied to the cardiac muscle," [3] and "more important than the quantity is the quality of the blood flowing through

[1] GASKELL: Journal of physiology, 1883, iv, p. 124.

[2] ROY and ADAMI: Philosophical transactions, 1892, clxxxiii, B, p. 290.

[3] MAGRATH and KENNEDY: Journal of experimental medicine, 1897, ii, pp. 13, 14.

the coronary vessels."[1] During any prolonged period of cardiac inhibition with a fall of blood-pressure in the aorta, the supply of nutriment to the heart muscle must certainly be diminished, and, as the right side of the heart is inhibited as well as the left, the arterialization of the blood must be diminished as well, and hence its quality deteriorated. So it seems very probable that any good effects upon the heart due to stimulation of trophic fibres may easily be counterbalanced by the injurious effects just pointed out. Hence a sudden and marked rise of pressure following inhibition is very probably due to some cause other than improvement in the nutrition of the heart. Moreover, this rise probably is not due to stimulation of the vaso-constrictor centre by a too venous condition of the blood; the rise occurs too suddenly to admit of such an explanation.

Whatever may prove to be the correct explanation of a rise of blood-pressure in some guinea-pigs after stimulation of the vagus, this rise is almost invariably followed immediately by a fall of blood-pressure below the normal, and very frequently by sudden failure of the heart and death of the animal. Fig. 3 is a tracing showing cardiac inhibition from stimulation of the vagus immediately after the animal had been prepared. After the cessation of the stimulation there took place a considerable rise of blood-pressure; the heart's beat became irregular, and the animal died within two minutes, death being preceded by a very rapid fall of blood-pressure. Throughout the whole series of my experiments stimulation of the vagi seemed to lessen the efficiency of the heart. This was especially true in the months from February to April, when the vitality of the animals was low, but it was also true in the months from October to January.

"*Escape*" *of the heart from vagus stimulation.* The heart of a guinea-pig when brought to a standstill by stimulation of the vagus soon begins to beat again; or, when slowed, to increase the frequency of its beats. The longest period during which I was able to maintain a standstill by stimulating the vagus was twenty-one seconds, and in this case death followed almost immediately, as was usually the case when the vagus nerve had been stimulated for any length of time in the spring. The following experiments illustrate the rate of escape during that season. I have no record of escape during the autumn, when the animals were in a more vigorous condition.

[1] FOSTER: Text-book of physiology, 6th ed., 1893, p. 367.

Experiment I. Guinea-pig; weight 550 grams; corrected mean blood-pressure 69 mm. of mercury; normal heart-rate 32 (all of the rates given are for periods of 10 seconds); peripheral end of right vagus stimulated while the secondary coil was at 15 cm. Rates during stimulation: $6\frac{1}{2}$, 9, 15, 16, 8, 6, death.

Experiment II. Guinea-pig; weight 637 grams; corrected mean blood-pressure 84 mm.; normal heart-rate 38; peripheral end of right vagus stimulated, secondary coil at 10 cm. Rates during stimulation: 3, 17, 15, 19, 25, 31, 35. The heart failed suddenly after the rate had increased to 35 and the blood-pressure had nearly reached the normal.

Effect of shunting the current from one vagus nerve to the other. It is an interesting question whether there be a single inhibitory mechanism in the heart or one for each vagus nerve. It is believed by many [1] that the same intracardiac apparatus serves for both nerves, — that after the heart of a mammal has begun to escape from inhibition produced by stimulation of one nerve, shunting the current into the other nerve does not cause a second standstill. I have found the contrary to be true in the guinea-pig, and have repeatedly caused a second standstill by suddenly shunting the current into the second nerve after escape had commenced from the inhibition caused by continued stimulation of the first nerve. This was tried, however, only in the spring months, when the cardiac-inhibitory mechanism was perhaps unusually irritable.

The following case has several features of interest: —

February 22, 1897. Guinea-pig; weight 510 grams. Chloral and morphine. Corrected mean blood-pressure 83 mm.; pulse-rate 37 in 10 seconds. Both vagi cut. Secondary coil at 12 cm. Stimulation of peripheral end of left vagus; heart stopped 10 seconds and blood-pressure fell to 26 mm.; heart's rate increased to 5 beats in 10 seconds and blood-pressure rose to 53 mm.; current shunted to right nerve; heart stopped 11 seconds and blood-pressure again fell to about 26 mm. The heart then rapidly increased in rate (the stimulation still continuing), gave a few irregular beats, and suddenly increased to 55 beats in 10 seconds, while the rate before stimulation had been only 37. Following a short period (12 seconds) of frequent beating, there occurred a period of infrequent irregular pulsations alternating with frequent beats. This state of things was allowed to continue for half a minute, when the current was shunted back into the left nerve; the heart was again stopped for four seconds. The heart's rate suddenly increased to 42 in 10 seconds,

[1] HÜFLER, E.: Die abgestufte Reizung des Herzvagus. Archiv für Physiologie, 1889, p. 295. HOUGH, *op. cit.*, p. 198.

when a short period of frequent and irregular beating was followed by failure of the heart and death of the animal, the stimulation having been maintained to the end. This is the only case in which acceleration was observed to occur during continued stimulation of the vagus. It is the only case in which acceleration was observed, except a few cases in which it appeared as an after-effect of inhibition.

The comparative efficiency of the two vagi. In a number of species of animals one vagus, usually the right, has been found to exert a more powerful influence upon the heart than does the other. In the guinea-pig I have found both vagi to be always efficient, and in no case have I been able to discover any greater efficiency on the part of one than on that of the other.

In quite a number of cases simultaneous stimulation of both vagi has not been observed to give more powerful inhibition than stimulation of the same strength applied to either nerve separately.

III. The Depressor Nerve.

There is found in the guinea-pig in close relation to the vagus and cervical sympathetic a very delicate nerve, stimulation of which causes a fall of blood-pressure resembling in every respect that caused by stimulating the depressor in the rabbit. This nerve can usually be found by raising the carotid artery out of its sheath on a curved

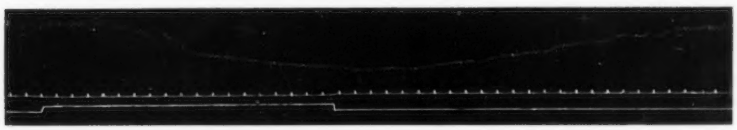

Figure 4. Three-fifths original size. Fall of blood-pressure as a result of stimulation of the central end of the left depressor with the secondary coil at 8 cm. Time in seconds. The line of zero pressure is not shown. The writing points of the manometer and of the stimulating key were in the same vertical line.

needle and thus putting the tissues between the carotid and the vagus on the stretch, the nerve is then seen extending through the connective tissue as a delicate whitish filament. At least part of this nerve can be traced to the ganglion of the trunk of the vagus, and in so far its origin resembles that of the depressor in the opossum;[1] whether, as in the opossum, there is a second root springing from the superior laryngeal nerve I have not been able to determine satisfactorily.

[1] Hunt and Harrington: *op. cit.*, p. 717.

Stimulation of the central end of this nerve gives results very similar to those observed when the depressor of the rabbit or of the opossum is stimulated, namely, a fall of blood-pressure (Fig. 4) and moderate slowing of the heart's rate if the vagi are intact.

A number of attempts were made to stimulate the various branches of the stellate ganglion to determine whether they contained cardiac accelerator nerves, but as this work was deferred until the spring, it was found that the animals did not possess sufficient vitality to permit the necessary dissection and prolonged experiment.

In conclusion I desire to express my indebtedness for valuable assistance and suggestions to Professor Frederic S. Lee and to Dr. Reid Hunt.

PHLORHIZIN DIABETES IN DOGS.

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IN a paper published[1] recently from this laboratory it was shown that when starving rabbits are kept under the constant influence of phlorhizin[2] by frequent subcutaneous administration of the drug, a constant relation approximating the ratio 2.8 : 1 is established between urinary dextrose and nitrogen, after the preliminary sweeping out of the systemic sugars through the urine. This ratio is the same as that already discovered by Minkowski in total pancreas diabetes in dogs. From the meagre experiments of others which could be used for comparison, the conclusion was drawn in the article just cited that like results would be obtained by treating dogs in a manner similar to that employed for rabbits. Various experiments preliminary to the present research, however, did not give the results expected. The ratio in dogs was found always higher than in rabbits, as is seen in the following table: —

DOG I. Weight 24.1 kg. 3 grams Phlorhizin every 8 hours.

Date.	Dextrose.	Nitrogen.	D : N	Food.
Jan. 5, 1897	53.07	11.54	4.51	. . . . .
6,	64.49	11.16	5.77	. . . . .
7,	61.63	16.29	3.78	. . . . .
8,	60.38	16.36	3.69	. . . .
9,	73.05	20.45	3.57	½ 30 grams meat per hour for 10 hours.

[1] LUSK, G., unter Mithilfe von E. L. MUNSON, E. A. LAWBAUGH, und I. M. HELLER: Zeitschrift für Biologie. 1898. xxxvi. p. 82. The general literature on the subject of phlorhizin diabetes is discussed in this article, and need not be restated here.

[2] This word is also spelled phloridzin and phlorizin, which are incorrect (Kulz und Wright, Zeitschrift für Biologie. 1890. xxvii. p. 181). Webster and the Century Dictionary give phlorizin, but the more correct spelling implied by the Greek derivative φλοιός ῥίζης demands the use of phlorhizin.

On account of the above experiment we came to the conclusion that the excess of sugar was removed in the dog more gradually than in the rabbit, and we decided to continue the constant influence of phlorhizin over a considerable period of time, with a view to the ultimate establishment of a ratio D : N : : 2.8 : 1. In this and in all the following experiments the dogs fasted two and a half to three days before the first administration of phlorhizin. In the following experiment, on the fifth day of diabetes and the seventh of fasting, the dog was so weak that it could not stand up and so 100 grams of lean meat cut free from fat was given thereafter every eight hours. The dog's condition greatly improved, and remained satisfactory until nearly the end of the experiment. On the last day it was not so weak as the day before we began to feed meat.

Phlorhizin warmed in a 1.2 per cent solution of sodium carbonate was injected subcutaneously every eight hours. [See Table, Dog II.]

It will be seen that the ratio 2.8 : 1 was not to be obtained on the eleventh day of phlorhizin diabetes in dogs, but that the ratio remained constantly higher. The same drug together with analytical reagents yielded upon the second day of an experiment on a fasting rabbit the ratio 2.89 : 1, and on the third day 2.69 : 1, ratios which are characteristic in the rabbit. The average ratio found in the dog during the last nine days was 3.75 : 1. No appreciable change in the ratio was brought about by feeding meat.

The total amount of dry fæces passed during the thirteen days was 67.35 grams, containing 3.02 grams of N or 4.20 per cent. This represents a daily amount of 0.23 grams of nitrogen. The fæces were pitch black, like hunger or meat fæces in dogs, and frequently here and in other experiments were accompanied by diarrhœa. This fact led sometimes to the mixing of urine and fæces, as may be noted in experiments still to be cited.

The sugar in the urine is dextrose, for it is completely fermentable with yeast, is only slightly affected by boiling with 8 per cent hydrochloric acid, and its specific rotation in the polariscope agrees with the reducing power determined according to the method of Allihn. Here then is a new level of sugar production from proteid. If we assume that 6.25 grams of proteid are burned for each gram of urinary nitrogen (neglecting that in the fæces), then 3.75 grams of dextrose may be derived from 6.25 grams of proteid, or approximately 60 per cent of dextrose from the molecule.

If instead of averaging the ratios of the last 8¼ days we take the

DOG II.

Date.	Amount of urine in cc.	Weight in kg.	Dextrose.	Nitrogen.	D : N.	Phlorhizin every 8 hours.	Food every 8 hours.
Mar. 5, 1897	?	21.4	....	4.04	....	....	....
6.	107	....	....	4.17	....	....	....
7.	640	....	63.55	12.66	5.02	2.5 grams	....
8.	546	....	65.30	18.76	3.48	"	....
9.	960	20.1	65.84	18.57	3.54	"	....
10.	1075	....	64.80	17.29	3.74	"	....
11.	1325	18.6	77.48	21.45	3.61	5 grams	100 gr. meat
12.	1490	....	71.12	18.17	3.91	"	"
13.	1492	....	66.71	18.30	3.64	2.5 grams	"
14.	1670	....	69.09	17.63	3.91	"	"
15.	1510	17.6	62.01	16.06	3.80	"	"
16.	1215	....	57.70	15.80	3.65	"	100 gr. meat + 25 gr. lard
17.	4301	17.2	16.90	4.54	3.72	"	100 gr. meat

1 63 hours' urine. Glycogen in the liver = 0.392 gr. = 0.68 per cent.

relation between the sum of the dextrose and nitrogen, we obtain 550.6 grams D : 147.8 grams N : : 3.72 : 1. By adding to this nitrogen that derived from the fæces ($8\frac{1}{4} \times 0.23$) we obtain the following ratio: 550.6 grams D : 149.7 grams N : : 3.67 : 1. According to this latter ratio the amount of sugar obtainable from proteid may be 58.7 per cent of the molecule.

This great sugar excretion is accompanied by a highly remarkable rise in the proteid metabolism above that in fasting. Thus on the third day of fasting 4.17 grams of nitrogen were eliminated, whereas

on the fifth day of fasting and the second of diabetes the nitrogen in the urine amounted to 18.76 grams, an increase of 450 per cent. Another experiment shows an increase of 540 per cent and two more an increase of 340 per cent each. A parallel to this rise in proteid metabolism is only to be found in the literature of phosphorus poisoning, and indeed the cause of the high metabolism, namely, the non-burning of the carbohydrates, would seem to be identical in the two cases. In the case of diabetes the sugar is removed and its well-known sparing influence over proteid metabolism is eliminated.[1] The explanation of the similar metabolism in phosphorus poisoning which seems most plausible to us is that the proteid sugar instead of being burned is converted quantitatively into fat, with the resulting high proteid metabolism noted in fatty degeneration. Experimental evidence upon this part of the subject is being now obtained.

It will be noted above that there is no difference in the sugar excretion whether 2.5 grams or 5 grams of phlorhizin be administered every eight hours.

Fat. — Feeding 25 grams of lard does not increase the sugar excretion, a result which was to be expected from the work of Moritz and Prausnitz.[2]

Behavior of Ingested Sugars. — The discovery of this intense form of diabetes in dogs led to the question of the behavior of different sugars after they had been fed to such dogs. In the following experiment 100 grams of lean meat was fed every eight hours from the fourth day of diabetes, and the dog being very fat bore the experiment extremely well. The idea was to obtain D : N : : 3.75 : 1, and then to feed the various monosaccharides which enter into physiological consideration, namely dextrose, levulose, and galactose. The "extra sugar" in the urine of these dogs can be estimated by multiplying the nitrogen in the urine by 3.75 (which represents sugar from proteid) and subtracting this from the total sugar found for the day. Any such "extra sugar" would be derived from the sugar fed. The sugar dissolved in water was readily taken by the dogs and was fed in portions of eight grams every six hours, commencing immediately after the urine had been drawn off in the morning.

[1] Lusk: *loc. cit.*, p. 97; also Lusk: Zeitschrift für Biologie, 1890, xxvii, p. 459.

[2] Moritz and Prausnitz: Zeitschrift für Biologie, 1890, xxvii, p. 81.

DOG III.—2 grams Phlorhizin every 6 hours after April 14.

Date.	Amount of urine in c.c.	Weight.	Dextrose.	D by polar.	Nitrogen.	D : N.	Extra sugar.	P_2O_5.	N : P_2O_5.	Food.
April 12, 1897	455	27.3	....	....	4.09	....	....	0.913	5.3	. . . . .
13,	288	....	....	....	2.79	....	....	0.485	5.7	. . . . .
14,	865	....	38.95	....	4.12	9.46	23.50	0.354	11.6	. . . . .
15,	1255	....	46.22	....	9.49	4.87	10.64	0.990	9.6	. . . . .
16,	1670	....	53.41	....	8.69	6.14	20.82	1.045	8.3	23.77 grams dextrose.
17,	1950	25.8	58.68	....	13.46	4.36	8.21	2.000	6.7	100 gr. meat every 8 hours.
18,	2000	....	50.29	....	12.90	3.89	....	2.185	5.9	" "
19,	2330	....	66.66	....	11.78	5.66	22.49	1.587	7.4	Meat + 24 gr. dextrose.
20,	1765	....	51.74	....	13.15	3.94	....	1.710	8.2	Meat.
21,	1872	25.0	63.27	57.5	12.79	4.95	15.31	1.531	8.3	Meat + 24.05 gr. levulose.
22,	1640	....	44.56	44.0	11.65	3.82	....	1.278	9.1	Meat.
23,	1885	....	51.85	49.4	11.85	4.37	7.42	1.352	8.8	Meat + 24.02 gr. levulose.
24,	1285	....	35.10	32.0	9.91	3.54	....	1.200	8.2	Meat.
25,	1820	24.9	51.59	50.6	11.65	4.43	7.89	1.650	7.0	Meat + 24 gr. galactose.
26,	1380	....	47.79	44.8	9.55	5.00	1.198	1.120	8.5	" "
27,	1355	....	41.61	39.1	10.39	4.00	....	1.292	8.0	Meat.
April 28, 1897 (8 hours' urine)	445	24.3	11.87	10.5	3.37	3.53	....	0.498	6.7	Meat.

Average of last six meat days — D : N :: 3.79 : 1. — Glycogen in liver — 0.936 grams = 0.31 %. — Glycogen in voluntary muscle = 0.37 %.

April 19, 20, and 21, the dog received one gram phlorhizin every three hours, except at 1 and 7 A.M., when 2 grams were given, and 4 A.M., when none was given.

Dextrose. On the first day of dextrose feeding, 20.82 grams of extra sugar was present in the urine, following an ingestion of 23.77 grams of dextrose. The experiment was however inconclusive, since the fasting ratio between dextrose and nitrogen had not been obtained. The day before the second feeding of dextrose, the ratio between dextrose and nitrogen was 3.89:1; on the sugar day, 5.66:1; and on the following day 3.94:1. The extra sugar here was 22.49 grams following an ingestion of 24 grams of dextrose. A third experiment is taken from the unpublished work of Messrs. T. S. McDermott and W. E. Ray done in this laboratory and is given below.

DOG IV. — Weight 10 kg. 1 gram Phlorhizin every 8 hours.

Date.	Dextrose.	Nitrogen.	D : N.	Extra sugar.	Food.
Nov. 18, 1897	36.72	9.63	3.81	....	. . . . .
19,	29.66	7.04	4.20	....	. . . . .
20,	48.40	10.29	4.70	9.82	{ 150 grams meat + 11.76 grams dextrose.
21,	41.52	10.89	3.81	....	150 grams meat.

Here we have on the sugar day a ratio of 4.70:1 and an excretion of 9.82 grams of extra sugar following upon an ingestion of 11.76 grams.

We can conclude from our experiments that the dextrose fed is very nearly quantitatively eliminated. These experiments prove also that, within these limits at least, very little loss takes place through fermentation.

Levulose. After feeding 24.05 grams of levulose, 15.31 grams of extra sugar appeared in the urine. The extra sugar could not be destroyed by heating the urine for several hours at 100° with 8 per cent hydrochloric acid. It therefore was not levulose. The reading in the saccharimeter was lower than it should be. Two causes might have contributed to this: first, the lævo-rotary substances of phlorhizin urines discovered by Cremer;[1] second, personal error, it being the first time this particular saccharimeter was used, and the solution being so weak that a difference of 0.2 per cent would account for the discrepancy between 63.27 grams and 57.5 grams.

[1] CREMER: Zeitschrift für Biologie, 1898, xxxvi. p. 115.

On the second feeding of 24.02 grams of levulose, 7.42 grams of extra sugar appeared in the urine, and here the totals of dextrose by Allihn's method and by polarization were respectively 51.85 and 49.4 grams. After ingestion of levulose is seen therefore its well-known partial conversion into dextrose, which in phlorhizin diabetes is quantitatively eliminated. It is especially remarkable that the burning levulose does not affect the proteid metabolism. Possibly the levulose may be burned by the sugar-hungry cells of the villus as soon as it is absorbed, and therefore its influence on metabolism is not widespread, but limited to certain localities. Minkowski[1] has shown that levulose if fed to diabetic dogs may increase the glycogen in the liver. In virtue of the small amounts of levulose used in our experiments, it seems improbable that it could reach the liver before combustion, and we would suggest that possibly the epithelium of the villus likewise may have the power for this conversion.

Galactose. Results similar to those obtained after feeding levulose were found on feeding galactose. In both cases of galactose feeding the extra sugar consisted of dextrose. This was determined by the fact that the specific rotation of the solution indicated the same amount of dextrose as was shown by the method of Allihn. For dextrose $(a)_D = +52.6°$, for galactose, $+83.8°$. Galactose may therefore in part be converted into dextrose.

Phosphates. — It has been stated by von Ackeren[2] that phosphates in diabetic urine are present above the amount normally pertaining to the proteid decomposition. The phosphates were therefore determined in the phlorhizin urine by titration with uranium nitrate. The results show that after fifteen days of diabetes there is no marked change from the usual ratio between phosphates excreted and proteid metabolism. This result is in confirmation of the experiments of Tenbaum[3] in diabetes mellitus, who also finds the calcium excretion to be unchanged.

Glycogen. — Phlorhizin diabetes fails to remove glycogen entirely from the liver and muscles. Glycogen in the liver of Dog II amounted to 0.392 grams = 0.08 per cent; in the liver of Dog III, 0.936 grams = 0.13 per cent, and in the muscle of the hind leg the large amount of 0.37 per cent was found. The dogs were killed while

[1] Minkowski: Archiv für exper. Pathol. und Pharmakol., 1893, xxxi, p. 165.

[2] Von Ackeren: See von Noorden: Pathologie des Stoffwechsels, 1893, p. 416.

[3] Tenbaum: Zeitschrift für Biologie, 1896, xxxiii, p. 379.

under the influence of morphine, which prevents loss of glycogen from struggling.

More frequent administration of phlorhizin, *i. e.*, once every three instead of once every six hours, does not change the ratio D : N in the urine.

Sugar production from Meat and Gelatine. — We have seen that feeding meat in small quantities during the day does not change the ratio D : N. Experiments were now tried with larger amounts of meat and with gelatine to seek for the ratio under these circumstances. On the days of meat feeding the urine was analyzed in fractions of equal periods, as will be described later. The general results for twenty-four hours urine are given below, two dogs having been experimented upon.

DOG V. — 1 gram Phlorhizin every 8 hours after Feb. 22.

Date.	Amount of urine in cc.	Weight in kg.	Dextrose.	Nitrogen.	D : N.	Food.
Feb. 22, 1898	76	12.8	....	2.49	....	. . . .
23,	393	....	40.36	6.88	5.84	. . . .
24,	555	....	47.47	13.49	3.52	. . . .
25,	625	....	47.73	14.01	3.41	. . . .
26,	1013	....	74.95	21.11	3.55	500 grams meat.
27,	576	....	42.32	11.53	3.67	. . . .
28,	910	....	53.17	14.52	3.66	60 grams gelatine.
Mar. 1, 1898	495	....	34.20	9.21	3.71	. . . .
2,	790	....	63.95	18.39	3.42	500 grams meat.
Mar. 3, 1898 (6 hours' urine)	84	10.6	6.93	1.68	4.12	. . . .
Average for last eight days: D : N :: 3.63 : 1. Rise in N excretion during starvation = 560 %.						

Before entering into the detailed discussion of the experiments, a few brief remarks on the theory of the method of proteid destruction within the organism would seem to be necessary. The well known theory of Voit [1] maintains that there is a preliminary cleavage of the

[1] Voit: Hermann's Handbuch der Physiologie, 1881, vi, 1, p. 295.

DOG VI. — 2 grams Phlorhizin every 8 hours after Feb. 6.

Date.	Amount of urine in c.c.	Weight in kg.	Dextrose.	Nitrogen.	D : N.	Food.
Feb. 3, 1898	....	36.71	....	....	....	. . . . .
6,	770	....	....	8.99	....	. . . . .
7,	1730	....	69.36	13.49	5.14	. . . . .
8,	2555	....	74.06	18.58	3.98	. . . . .
9,	2895	....	69.72	18.04	3.86	. . . . .
10,	3270	....	79.66	23.79	3.30	105 grams gelatine.
11,	2160	....	50.23	14.66	3.42	. . . . .
12,	4181	....	85.94	27.49	3.13	870 grams meat.
13,	1970	....	52.11	12.44	4.19	. . . . .
14,	2860[1]	....	41.60	19.67	2.11	105 grams gelatine.
15,	2260	....	29.40	11.73	2.70	. . . .
16,	B 1528[2]	....	22.43	6.80	3.31	20 grams levulose.
	A 238[3]	....	4.58	1.65	2.77	. . . . .
17,	570[4]	27.7	7.23	2.37	3.05	. . . . .

[1] Albuminuria.
[2] 16 hours' urine.
[3] Some lost through mixture with fæces.
[4] 6 hours' urine.

proteid molecule in metabolism into a nitrogenous radicle, and into a non-nitrogenous radicle, each of which may subsequently be burned within the cells at different times. The experiments of Feder [1] have shown that after feeding meat to a starving dog the quantity of nitrogen in the urine rises, attaining a maximum at the sixth to the eighth hour, and then continuously sinks, so that at the fourteenth hour most of the nitrogen corresponding to the meat eaten has been eliminated. The excretion of CO_2 under these circumstances is, however, much more evenly distributed over the course of the twenty-four hours. Voit [2] concludes therefore that there is an early cleavage of the proteid molecule through which little energy is liberated; that there is a rapid combustion of the nitrogenous radicle, as shown by the elimination of the nitrogenous end products in the urine;

[1] Feder: Zeitschrift fur Biologie, 1881, xvii, p. 541.
[2] Voit: Zeitschrift fur Biologie, 1891, xxviii, p. 291.

and that the non-nitrogenous radicle which contains the major part of the potential energy of the molecule may in part be temporarily stored either as glycogen or as fat, and be fed to the tissues more evenly during the course of the twenty-four hours as need requires. Now the indications are that phlorhizin acts quickly, removing sugar from the organism as soon as it is produced. If Voit's non-nitrogenous portion of the proteid consist of dextrose and the idea of its quick cleavage from proteid be true, then on feeding meat to a phlorhizin dog more sugar should appear in the urine of the first hours after feeding than corresponds to the nitrogen eliminated.

The results of one experiment after feeding 500 grams of meat to a fasting diabetic dog, and collecting the urine first in two periods of three hours each, and then in one of six hours, are given below. The urine was, of course, obtained through a catheter and the bladder was carefully washed with water. The meat was eaten within one minute.

DOG V. — Urine of Feb. 26.

	Amount in cc.	Dextrose.	Nitrogen.	D : N.
Preceding 3 hours (estimated) . .	....	5.96	1.75	3.41
1st 3 hours	137	12.43	2.52	4.92
2d 3 hours	193	14.70	3.76	3.91
3d 3 hours	385	11.23	3.85	2.92
4th 3 hours		11.23	3.85	2.92
Following 3 hours (estimated) . .	....	6.34	1.78	3.56

We start here with the estimated decomposition during three hours of fasting. During three hours after feeding meat the ratio in the urine equals D : N : : 4.92 : 1, and in a subsequent period of three hours the ratio reads 3.91 : 1, whereas during the next six hours it sinks to 2.92 : 1. This however is followed by a period in which the original fasting quantity of dextrose and nitrogen with the original ratio are approximately attained. If we take the whole period of twelve hours when meat was fed and compare it with the foregoing and following periods of like duration we discover the following relations: —

	Dextrose.	Nitrogen.	D : N.
Fasting, 12 hours (estimated) . .	23.87	7.00	3.41
After meat feeding, 12 hours . .	49.59	14.00	3.54
Subsequent 12 hours	25.36	7.11	3.56

Since the meat period of twelve hours was followed by a period entirely similar to the fasting period from which the start was made, it follows that the meat was absorbed and burned almost entirely within the first twelve hours after feeding. And this table shows that in the aggregate the ratios D : N in all three periods are the same.

The sugar of eaten proteid is therefore entirely eliminated in phlorhizin diabetes, but it may be eliminated before the nitrogen belonging to it. Hence it is probably one of the more immediate cleavage products of the proteid molecule in metabolism.

It is impossible at the present writing to state whether the sugar in the urine of the above periods of three hours represents the amount of sugar formed within the three hours, and immediately eliminated, or whether the sugar excretion represents the maximum limit of renal activity, and hence its comparatively even distribution over the hours named.

The ability to gradually eliminate the sugar formed was illustrated in two experiments similar to the above but somewhat less satisfactory in their results. One was a subsequent experiment four days later on the same dog, when the general tone of the animal was less favorable. That the absorption and destruction of the meat within twelve hours was not due to special accident in the first experiment is shown by the fact still to be discussed that the dog was able to repeat the performance with 60 grams of gelatine two days later. In the meat experiment on dog VI the animal was not very strong, and subsequent to the experiment the ratio fell to approximately 2.8 : 1, which, as will be explained later probably indicates a decreased power of the kidneys. The conditions in the following two experiments were therefore distinctly less favorable for the quick removal of sugar through the kidney. That certain amounts of sugar may be protected from combustion in the organism is illustrated by the experiment on a fasting diabetic rabbit, whose urinary sugar was increased

after convulsions (which brought about a conversion of glycogen into sugar) this sugar being eliminated not immediately within the first hour, but gradually during six hours.[1]

The following results have been obtained from the urines of meat-fed dogs after dividing the urine into separate portions corresponding to two hours each. Dog V received 500 grams of meat, Dog VI 870 grams at one meal.

	Dog V.			Dog VI.		
	Urine of March 2.			Urine of Feb. 12.		
	D.	N.	D : N.	D.	N.	D : N.
Preceding 2 hours (estimated)	2.85	0.77	3.71	4.18	1.22	3.42
1st 2 hours	5.82	0.78 [1]	7.49	9.26	1.92	4.82
2d 2 hours	6.86	1.69	4.05	11.04	2.97	3.72
3d 2 hours	7.39	2.29	3.18	4.69 [2]	1.82	2.58
4th 2 hours	6.77	2.60	2.60	7.74	3.57	2.17
5th 2 hours	7.03	2.28	3.08	11.37	3.50	2.17
6th 2 hours	6.72	2.15	3.12	7.44	3.11	2.39
Following 2 hours (estimated)	3.89	0.98	3.95	5.72	1.60	3.25

[1] The urine of the first ten minutes was voided outside the cage and lost.
[2] A part of the urine was lost through admixture with fæces.

The curve of nitrogen excretion is not essentially different from that obtained by Feder in normal fasting dogs after feeding meat. In the first two hours in both of the above experiments we find a large quantity of sugar in the urine showing the high ratios 7.49 : 1 and 4.82 : 1. The complete excretion of the sugar, however, extends over some little time, which is probably due to deficient power of the kidney to remove the sugar, as has been explained above.

[1] Lusk : Zeitschrift für Biologie, 1898, xxxvi, p. 82. Dextrose fed to rabbits in large excess is burned in phlorhizin diabetes. The protecting power is therefore limited. Whether a similar power to burn carbohydrates when fed in excess is present in total phlorhizin diabetes in dogs is at present unknown to us.

For further clearness the following summary is added: —

	Dog V.			Dog VI.		
	D.	N.	D : N.	D.	N.	D : N.
Fasting 12 hours	17.10	4.60	3.71	25.11	7.33	3.42
Meat 12 hours	40.59	12.49	3.25	51.54	16.89	3.04
Following 12 hours . . .	23.36	5.90	4.12	34.40	10.60	3.25
Following 6 hours	6.93	1.68	3.95	. . . .	. . . .	. . .
Following 24 hours . . .	. . . .	. . . .	. . . .	52.11	12.44	4.19
Total subsequent to meat . .	70.88	20.07	3.53	138.05	39.93	3.45

These experiments, especially the first one made on Dog V, give a full confirmation of Voit's views. There is a quick preliminary cleavage of proteid into sugar and an unknown nitrogenous radicle. The sugar amounts to about 60 per cent of the proteid molecule, and contains not far from 60 per cent of its physiologically available energy. Through the action of phlorhizin the dextrose may be rapidly removed, whereas normally it is a substance which in excess may be stored as glycogen, or may even contribute to the formation of fat, both of which substances may be subsequently burned in the cells as need requires.

Absence of Putrefaction. — The fact that, generally speaking, in the cases of phlorhizin diabetes in dogs, there is no appreciable change in the ratio D : N, whether meat be fed or whether the dog be fasting, would indicate complete absence of putrefaction, for it is hardly possible that sugar could be produced within the organism from leucin, tyrosin, and other amido bodies formed in putrefaction.

Exceptional Cases. — We have remarked in the case of Dog VI the decrease in the ratio D : N to the basis found in rabbits of 2.8 : 1. This was accompanied by albuminuria. Only one other similar case has come to our notice, and that is taken from the work of Messrs. McDermott and Ray, done in this laboratory upon a fasting dog. The dog weighed 8.5 kg., and like the former dog had albumin in the urine.

The albuminuria suggests renal disease, but why, in the apparent absence of any chemical difference, one fraction of the sugar in pro-

teid should behave differently from the other fraction, remains a mystery. This peculiarity seems to bring added proof of the at least partially renal character of phlorhizin diabetes noted by Zuntz.[1] Phlorhizin diabetes cannot be wholly renal in character, for some unknown influence must protect sugar from combustion.

DOG VII.—1 gram Phlorhizin every eight hours after Dec. 19.

	Dextrose.	Nitrogen.	D : N.
Dec. 19, 1897	....	3.23	....
20, ...	29.51	7.34	4.02
21, 18 hours	28.34	10.36	2.73
8 hours	8.15	2.84	2.86
22, 16 hours	15.64	5.39	2.90

Gelatine. — It has already been shown in work on the rabbit[2] that both nitrogen and sugar rise in the urine after feeding gelatine, and that nearly the proteid ratio is maintained between the two. More exact determinations have been possible with dogs, and among several attempted by us may be mentioned the two following. In the first case 105 grams of French gelatine (containing 14.91 grams N), and in the second case 60 grams (8.52 grams N) were fed. The gelatine was stirred into hot water and on cooling was broken in fragments and moistened with water containing 0.5 — 0.3 grams meat extract (= 0.05 — 0.03 grams N). The mass was eaten greedily. In the first experiment the day commenced at 8.45 A. M., and at 9.15 A. M. about one quarter of the gelatine was eaten, at 3 P. M. about one half, and the remainder at 4.55 P. M. In the second experiment the whole mass was eaten at one time immediately at the commencement of the day.

Both of these experiments show an increased elimination of sugar and nitrogen after feeding gelatine. In the first experiment the ratio D : N fell from 3.86 in fasting to 3.30 on the gelatine day and rose to 3.42 on the following fasting day. The results in the second experiment are more convincing because here the ratio hardly changes in the two fasting periods, and it will be noticed that it also remains

[1] Zuntz: Archiv für Physiologie, 1895, p. 570.

[2] Lusk: *loc. cit.*

Dog VI.	Dextrose.	Nitrogen.	D : N.	Food.
Feb. 9, 1898	69.72	18.04	3.86	. . . . .
10.	79.66	23.78	3.30	105 grams gelatine.
11.	50.23	14.66	3.42	. . . . .
Dog V.	**Dextrose.**	**Nitrogen.**	**D : N.**	**Food.**
Feb. 27, 1898, 12 hours (estimated)	21.16	5.76	3.67	. . . . .
28. { 12 hours	35.85	9.70	3.69	60 grams gelatine.
28. { 12 hours	17.32	4.82	3.59	. . . . .
Mar. 1, 1898, 12 hours (estimated)	17.10	4.60	3.71	. . . . .

unaltered during the intervening period when gelatine was fed. We may therefore conclude that the same large percentage of dextrose is obtainable from the metabolism of gelatine as from proteid. In this second experiment the whole of the gelatine was apparently absorbed and destroyed within twelve hours after feeding, because the amount of nitrogen is similar in each of the fasting periods. A very considerable amount of proteid was evidently spared from destruction by the burning gelatine. The twelve hours urine after gelatine feeding shows the presence of 9.7 grams of N. The gelatine contained 8.4 grams N, and if 8 grams of this appeared in the urine, then an amount of proteid corresponding to only 1.7 grams N would have been burned during the twelve hours against 5.76 grams N found for the twelve hours preceding. This would indicate a sparing of proteid to the extent of 69 per cent by the gelatine. The considerable sparing power of burning gelatine over proteid is well known.

Theoretical Considerations as to the Constitution of Proteid. — The discovery that the proteid molecule yields on cleavage in metabolism an amount of sugar equal to 58.7 per cent (as near as we have been able to determine) leaves on the other hand a nitrogen-containing radicle in which the carbon and nitrogen would appear in the atomic ratio of 2.2 of C to 1 of N. It is evident from this that the nitrogenous radicle cannot in metabolism yield much leucin or tyrosin, which require much carbon, whereas glycocoll and the sulphur-con-

taining taurin are theoretically possible. It will further be remembered that modern theory regarding the synthesis of proteid in plants, supposes the formation of proteid from sugar through union with asparagin and glutamin. Asparagin contains 2 of C, glutamin $2\frac{1}{2}$ of C to 1 of N. It is also impossible to ignore the fact that the carbohydrate portion may be even larger than 58.7 per cent, and may possibly contain the radicles of levulose, of galactose, or even of pentoses, substances which may in part escape elimination in phlorhizin diabetes. Again, there is evidence that the glucoside phlorhizin which yields dextrose in the laboratory is destroyed in the body. Hence the sugar of all compounds of dextrose, even in phlorhizin diabetes, may not appear in the urine.

Summary.

1. Frequent subcutaneous injections of phlorhizin in fasting dogs establish ultimately the ratio in the urine of Dextrose: Nitrogen:: 3.75 : 1, which indicates a production of 60 grams of dextrose from 100 grams of proteid. Taking the fæcal nitrogen into consideration, the amount of dextrose obtained from proteid may be more accurately estimated at 58.7 per cent.

2. The proteid metabolism may increase above that in simple fasting to an extent as high even as 560 per cent.

3. Dextrose fed in phlorhizin diabetes is quantitatively eliminated. Levulose and galactose are not eliminated as such, but only in so far as they are converted into dextrose.

4. Feeding fat does not affect the ratio.

5. Feeding meat does not affect the ratio for the day, but the sugar from eaten proteid may be eliminated before the nitrogen belonging to it, on account of an early preliminary cleavage of the molecule.

6. Gelatine yields the same amount of sugar as proteid does. Gelatine spares much proteid from metabolism.

7. Intestinal putrefaction and fermentation can only slightly have affected the proteid or dextrose which were fed in our experiments.

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ON INTESTINAL ABSORPTION AND THE SALINE CATHARTICS.[1]

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IN his well-known paper on the absorption of salt solutions from the intestine Heidenhain[2] came to the conclusion that two distinct factors were involved in the process, — the osmotic pressure of the solution, and the "physiological activity" of the epithelium. The latter induces a constant current from the lumen of the bowel towards the blood vessels.

Hamburger[3] accepts Heidenhain's account of the osmotic action, but attempts to show that his "physiological activity" is really a combination of the effects of certain physical forces. These are molecular imbibition; the intra-intestinal pressure, which induces filtration; and the suction induced by the blood current through the intestinal vessels, similar to that observed with the ordinary suction pump of the laboratory. Hamburger's explanation of the intestinal absorption therefore involves an obscure process — the molecular imbibition — but differs from Heidenhain's in not involving the living cell.

Heidenhain performed a few experiments with solutions of the saline cathartic magnesium sulphate, from which he found that the water was much more slowly absorbed than from corresponding solutions of sodium chloride. He explains this retarded absorption by supposing that the sulphate lessens the "physiological activity" and that movement of its solutions is therefore controlled more by

[1] Received by the editors May 5, 1898.

[2] HEIDENHAIN: Arch. f. d. ges. Physiol., 1894, lvi, p. 579.

[3] HAMBURGER: Archiv für Physiologie, 1896, p. 428.